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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. **AP138-X** Total Pages **99**

First Named Inventor or Application Identifier

Gregory S. Hamilton

Express Mail Label No.

**APPLICATION ELEMENTS**

See MPEP chapter 600 concerning utility patent application contents.

1. Fee Transmittal Form
(Submit an original, and a duplicate for fee processing)
2. Specification [Total Pages **96**] (preferred arrangement set forth below)
 - Descriptive title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. Drawing(s) (35 USC 113) [Total Sheets **3**]
4. Oath or Declaration [Total Pages **2**]
 - a. Newly executed (original or copy)
 - b. Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed) [Note Box 5 below]
 - i. **DELETION OF INVENTOR(S)** Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. Incorporation By Reference (useable if Box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

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6. Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. Computer Readable Copy
 - b. Paper Copy (identical to computer copy)
 - c. Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. Assignment Papers (cover sheet & document(s))
9. 37 CFR 3.73(b) Statement Power of Attorney (when there is an assignee)
10. English Translation Document (if applicable)
11. Information Disclosure Statement (IDS)/PTO-1449 Copies of IDS Citations
12. Preliminary Amendment
13. Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
14. Small Entity Statement filed in prior application, Statement(s) Status still proper and desired
15. Certified Copy of Priority Document(s) (if foreign priority is claimed)
16. Other:

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:

 Continuation Divisional Continuation-in-part (CIP)
of prior application No: **60,087,843****18. CORRESPONDENCE ADDRESS** Customer Number or Bar Code Labelor Correspondence address below

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Attorney Docket No. AR138-X

MULTIPLE HETEROATOM CONTAINING HETEROCYCLIC RING COMPOUNDS
SUBSTITUTED WITH CARBOXYLIC ACIDS AND ISOSTERES THEREOF

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MULTIPLE HETEROATOM CONTAINING HETEROCYCLIC RING COMPOUNDS
SUBSTITUTED WITH CARBOXYLIC ACIDS AND ISOSTERES THEREOF

Related Application Data

5 This application is a continuation-in-part of U.S. patent application serial number 60/087,843 to Hamilton et al., entitled "Carboxylic Acids and Carboxylic Acid Isosteres of Heterocyclic Ring Compounds Having Multiple Heteroatoms", filed June 3, 1998.

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BACKGROUND OF THE INVENTION

15 1. **Field of Invention**

This invention relates to novel carboxylic acids and isosteres of heterocyclic ring compounds which have multiple heteroatoms within the heterocyclic ring, novel derivatives of these carboxylic acids and isosteres containing N-linked diketos, sulfonamides, ureas and carbamates attached thereto, and their preparation and use for treating neurological disorders including physically damaged nerves and neurodegenerative diseases, as well as for treating alopecia and promoting hair growth.

20 2. **Description of Related Art**

25 It has been found that picomolar concentrations of an immunosuppressant such as FK506 and rapamycin stimulate neurite outgrowth in PC12 cells and sensory neurons, namely dorsal root ganglion cells (DRGs). Lyons et al., *Proc. of Natl. Acad. Sci.*, 1994 vol. 91, pp. 3191-3195. In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury and results in functional recovery in animals with sciatic nerve lesions.

30 Several neurotrophic factors affecting specific neuronal populations in the central nervous system have been

identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed to treat Alzheimer's patients with exogenous nerve growth factor or other neurotrophic proteins such as brain derived nerve factor (BDNF), glial derived nerve factor, ciliary neurotrophic factor, and neurotropin-3 to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when administered chronically, immunosuppressants exhibit a number of potentially serious side effects including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., 1991, *J. Am. Soc. Nephrol.* 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina such as non-localized headaches (De Groen et al., 1987, *N. Engl. J. Med.* 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., 1989 *N. Engl. J. Med.* 321: 1725).

Accordingly, there is a need for small-molecule compounds which are useful for providing neurotrophic effects and for treating neurodegenerative disorders.

Hair loss occurs in a variety of situations. These situations include male pattern alopecia, alopecia senilis, alopecia areata, diseases accompanied by basic skin lesions or tumors, and systematic disorders such as nutritional disorders and internal secretion disorders. The mechanisms causing hair loss are very complicated, but in some instances can be attributed to aging, genetic disposition, the activation of male hormones, the loss of blood supply to hair

follicles, and scalp abnormalities.

The immunosuppressant drugs FK506, rapamycin and cyclosporin are well known as potent T-cell specific immunosuppressants, and are effective against graft rejection after organ transplantation. It has been reported that topical, but not oral, application of FK506 (Yamamoto et al., J. Invest. Dermatol., 1994, 102, 160-164; Jiang et al., J. Invest. Dermatol. 1995, 104, 523-525) and cyclosporin (Iwabuchi et al., J. Dermatol. Sci. 1995, 9, 64-69) stimulates hair growth in a dose-dependent manner. One form of hair loss, alopecia areata, is known to be associated with autoimmune activities; hence, topically administered immunomodulatory compounds are expected to demonstrate efficacy for treating that type of hair loss. The hair growth stimulating effects of FK506 have been the subject of an international patent filing covering FK506 and structures related thereto for hair growth stimulation (Honbo et al., EP 0 423 714 A2). Honbo et al. discloses the use of relatively large tricyclic compounds, known for their immunosuppressive effects, as hair revitalizing agents.

The hair growth and revitalization effects of FK506 and related agents are disclosed in many U.S. patents (Goulet et al., U.S. Patent No. 5,258,389; Luly et al., U.S. Patent No. 5,457,111; Goulet et al., U.S. Patent No. 5,532,248; Goulet et al., U.S. Patent No. 5,189,042; Ok et al., U.S. Patent No. 5,208,241; Rupprecht et al., U.S. Patent No. 5,284,840; and Organ et al., U.S. Patent No. 5,284,877). These patents claim FK506 related compounds. Although they do not claim methods of hair revitalization, they disclose the known use of FK506 for effecting hair growth. Similar to FK506 (and the claimed variations in the Honbo et al. patent), the compounds claimed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds for use in autoimmune related diseases, for which FK506's efficacy is well known.

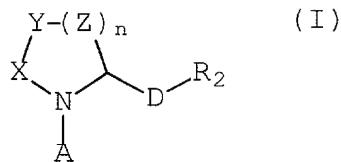
Other U.S. patents disclose the use of cyclosporin and related compounds for hair revitalization (Hauer et al., U.S. Patent No. 5,342,625; Eberle, U.S. Patent No. 5,284,826; and Hewitt et al., U.S. Patent No. 4,996,193). These patents 5 also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin and related immunosuppressive compounds for hair growth.

However, immunosuppressive compounds by definition suppress the immune system and also exhibit other toxic side 10 effects. Accordingly, there is a need for small molecule compounds which are useful as hair revitalizing compounds.

SUMMARY OF THE INVENTION

The present invention is directed to novel carboxylic acids and isosteres of heterocyclic ring compounds which have multiple (i.e. two or more) heteroatoms within the heterocyclic ring, novel derivatives of these carboxylic acids and isosteres containing N-linked diketos, sulfonamides, ureas and carbamates attached thereto, and their preparation and use for treating neurological disorders including physically damaged nerves and neurodegenerative diseases, as well as for treating alopecia and promoting hair growth. These compounds stimulate neuronal regeneration and outgrowth and as such are useful for treating neurological disorders and neurodegenerative diseases. These compounds 20 also promote hair growth and as such are useful for treating hair loss disorders. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity and/or are non-immunosuppressive. 25 30

A preferred embodiment of this invention is a compound having the formula (I):



where

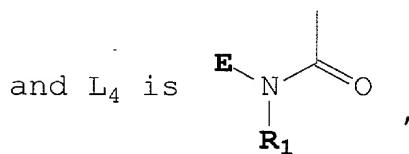
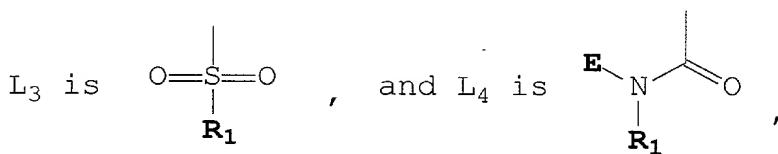
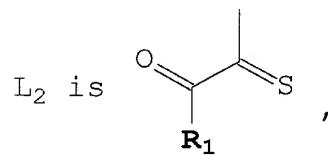
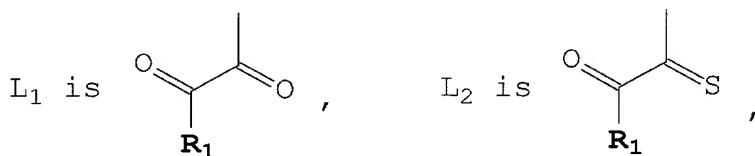
X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

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n is 1-3;

A is selected from the group consisting of L₁, L₂, L₃, or L₄,

where



R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉ straight or branched chain alkyl or alkenyl, C₂-C₉ straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

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D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

R₂ is carboxylic acid or a carboxylic acid isostere;

wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R³, where

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R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl,

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C_2-C_6 straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO_2R^4 where R^4 is hydrogen or C_1-C_9 straight or branched chain alkyl or alkenyl; or a pharmaceutically acceptable salt, ester, or solvate thereof;

provided that:

R_1 is not substituted with both hydroxy and oxygen to form carboxy, or R_1 is not substituted with both alkoxy and oxygen to form alkoxycarbonyl, or R_1 is not substituted with both amine and oxygen to form amide;

further provided that:

when A is L_1 or L_2 , and D is a bond,

then R_2 is not COOH, or an amide;

further provided that:

when A is L_1 , and R_1 is methyl, and D is a bond,

then R_2 is not COOH;

further provided that:

when A is L_3 , and R_1 is phenyl, methylphenyl, phenylmethyl, substituted or unsubstituted phenoxyphenyl, substituted naphthyl, or methoxyphenyl, and D is a bond,

then R_2 is not COOH or an amide;

further provided that:

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then R_2 is not thiophenyl;

further provided that:

when A is L_3 , and R_1 is

then R_2 is not an amide;

further provided that:

when A is L_3 , and R_1 \vdash

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when A is L_3 , and R₁ is substituted isoquinoline, and D is butyl,

then R_1 is not an amide;

further provided that:
when A is L_3 or L_4 , and R_1 is unsubstituted or substituted

hydrogen, and δ is the δ_1 of the amide.

further provided that:

when A is L_4 , and R_1 is phenyl, halo-substituted phenyl, dimethylphenyl, carboxy-substituted alkyl, substituted butyl, or methylphenyl, and D is a bond,

5 then R_2 is not COOH;

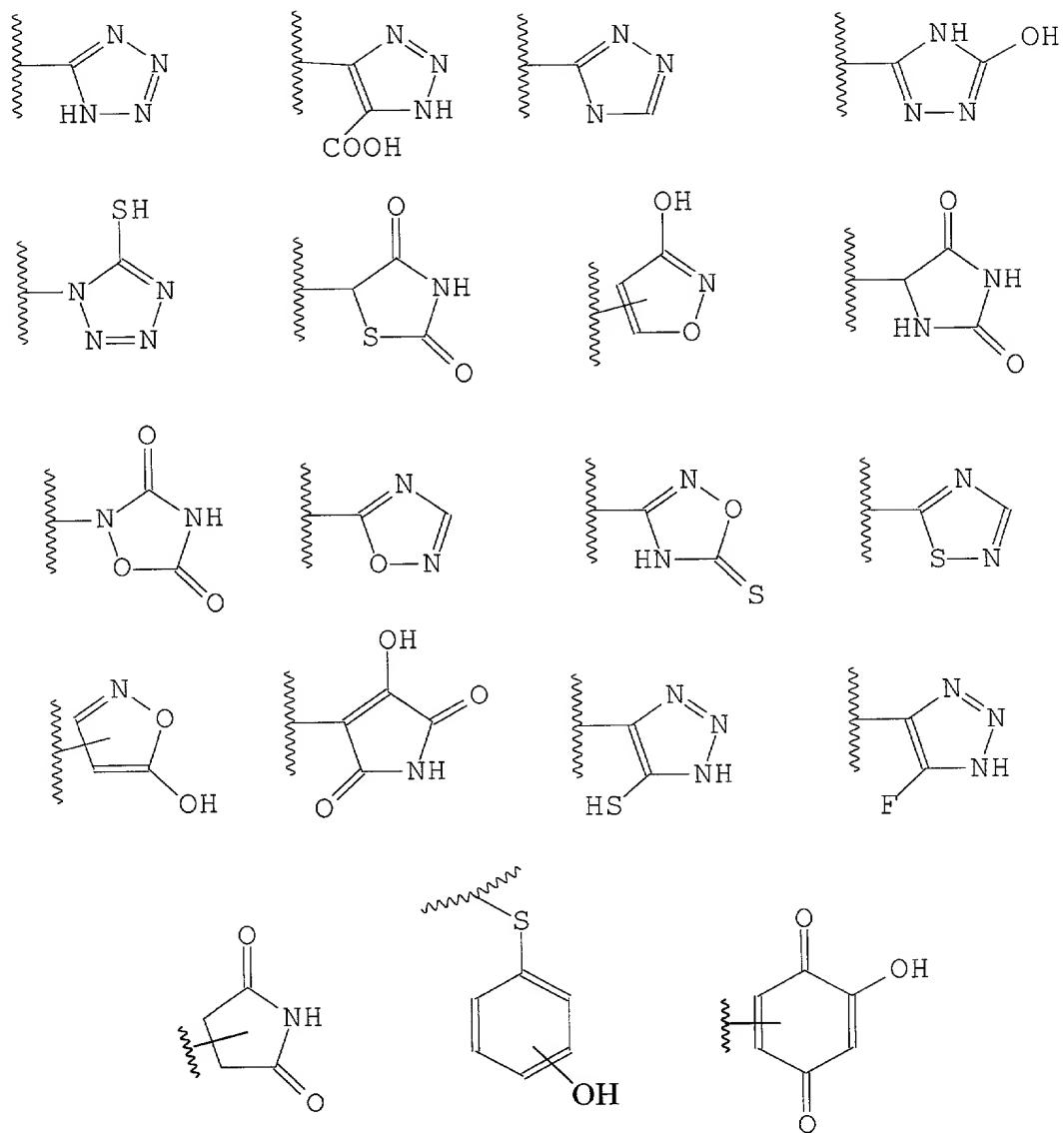
further provided that:

when A is L_4 , and R_1 is cyano-substituted alkyl, and D is a bond,

then R_2 is not an amide.

10 Preferred embodiments of this invention are where R_2 is a carbocycle or heterocycle containing any combination of CH_2 , O , S , or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions with R^3 .

Especially preferred embodiments of this invention are where R_2 is selected from the group below:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3 .

Another preferred embodiment of this invention is where 5
 R_2 is selected from the group consisting of
 $-COOH$, $-SO_3H$, $-SO_2HNR^3$, $-PO_2(R^3)_2$, $-CN$, $-PO_3(R^3)_2$, $-OR^3$, $-SR^3$,
 $-NHCOR^3$, $-N(R^3)_2$, $-CON(R^3)_2$, $-CONH(O)R^3$, $-CONHNHSO_2R^3$,
 $-COHNSO_2R^3$, and $-CONR^3CN$.

Preferred embodiments of this invention are the 10 neurotrophic compounds (2S)-1-(phenylmethyl)carbamoyl-2-hydroxymethyl (4-thiazolidine); (2S)-1-(1,1-dimethylpropyl)carbamoyl-2-(4-thiazolidine)tetrazole; and (2S)-1-(phenylmethyl) carbamoyl-2-(4-thiazolidine) carbonitrile.

Another preferred embodiment of this invention is a 15 pharmaceutical composition containing: an effective amount of a compound of formula (I); and a pharmaceutically suitable or acceptable carrier. For neurotrophic compositions a neurotrophic factor different from formula (I) may also be administered or otherwise included in the composition.

Another preferred embodiment of the invention is a 20 method of promoting neuronal regeneration and growth in mammals, comprising administering to a mammal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring.

Another preferred embodiment of the invention is a 25 method of treating a neurological disorder in an animal, comprising administering to an animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration.

Yet another preferred embodiment of the invention is a 30 method of preventing neurodegeneration in an animal, comprising administering to an animal an effective amount of

a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring.

Yet another preferred embodiment of the invention is a method of treating alopecia or promoting hair growth in an animal, comprising administering to an animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a photograph of C57 Black 6 mice before being shaved for the hair regeneration experiment.

Figure 2 is a photograph of mice treated with a vehicle after six weeks. Figure 2 shows that less than 3% of the shaved area is covered with new hair growth when the vehicle (control) is administered.

Figure 3 is a bar graph illustrating relative hair growth on shaved mice treated with N-heterocyclic carboxylic acids or carboxylic acid isosteres at 1umole per milliliter three times per week. Hair growth was evaluated after 14 days of treatment.

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DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" means a branched or unbranched saturated hydrocarbon chain comprising a designated number of carbon atoms. For example, a C₁-C₆ straight or branched alkyl hydrocarbon chain contains 1 to 6 carbon atoms, and includes but is not limited to substituents such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, and the like. It is also contemplated as within the scope of the present invention that "alkyl" may also refer to a hydrocarbon chain wherein any of the carbon atoms of said

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alkyl are optionally replaced with O, NH, S, or SO₂. For example, carbon 2 of n-pentyl can be replaced with O to form propyloxymethyl.

"Alkenyl" means a branched or unbranched unsaturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C₂-C₆ straight or branched alkenyl hydrocarbon chain contains 2 to 6 carbon atoms having at least one double bond, and includes but is not limited to substituents such as ethenyl, propenyl, iso-propenyl, butenyl, iso-butenyl, tert-butenyl, n-pentenyl, n-hexenyl, and the like. It is also contemplated as within the scope of the present invention that "alkenyl" may also refer to an unsaturated hydrocarbon chain wherein any of the carbon atoms of said alkenyl are optionally replaced with O, NH, S, or SO₂. For example, carbon 2 of 4-pentene can be replaced with O to form (2-propene)oxymethyl.

"Alkoxy" means the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms.

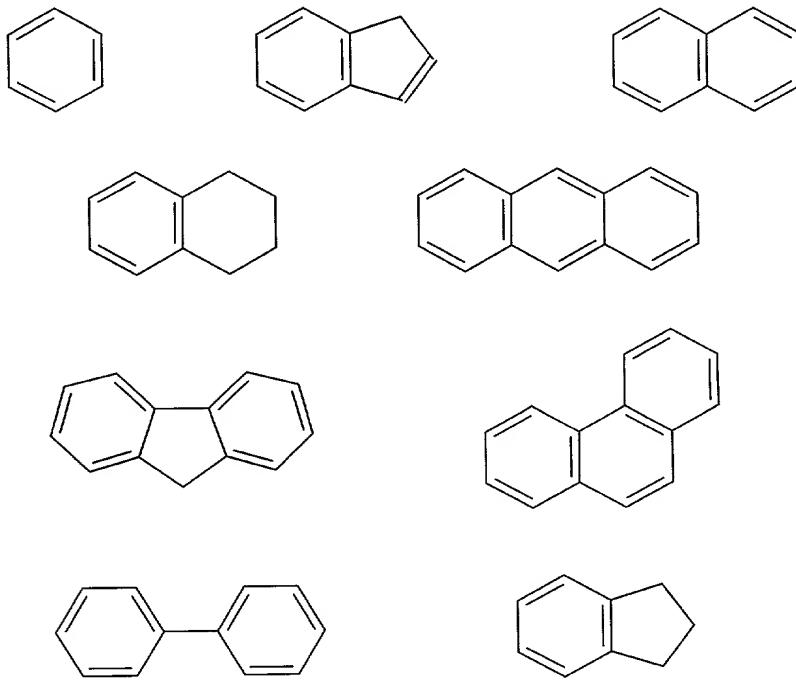
The term "carbocycle" refers to an organic cyclic moiety in which the cyclic skeleton is comprised of only carbon atoms whereas the term "heterocycle" refers to an organic cyclic moiety in which the cyclic skeleton contains one or more heteroatoms selected from the group comprising nitrogen, oxygen, or sulfur and which may or may not include carbon atoms.

Thus, the term "carbocycle" refers to a carbocyclic moiety containing the indicated number of carbon atoms. The term "C₃-C₈ cycloalkyl", therefore, refers to an organic cyclic substituent in which three to eight carbon atoms form a three, four, five, six, seven, or eight-membered ring, including, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl ring. As used herein, "carbocycle" may also refer to two or more cyclic ring systems which are fused to form, for example

bicyclic, tricyclic, or other similar bridged substituents (e.g. adamantyl).

5 "Aryl" refers to an aromatic carbocyclic group having a single ring, for example a phenyl ring; multiple rings, for example biphenyl; or multiple condensed rings in which at least one ring is aromatic, for example naphthyl, 1,2,3,4-tetrahydronaphthyl, anthryl, or phenanthryl, which can be unsubstituted or substituted with one or more other substituents as defined above. The substituents attached to a phenyl ring portion of an aryl moiety in the compounds of 10 Formula (I) may be configured in the ortho-, meta-, or para- orientations.

15 Examples of typical aryl moieties included in the scope of the present invention may include, but are not limited to, the following:



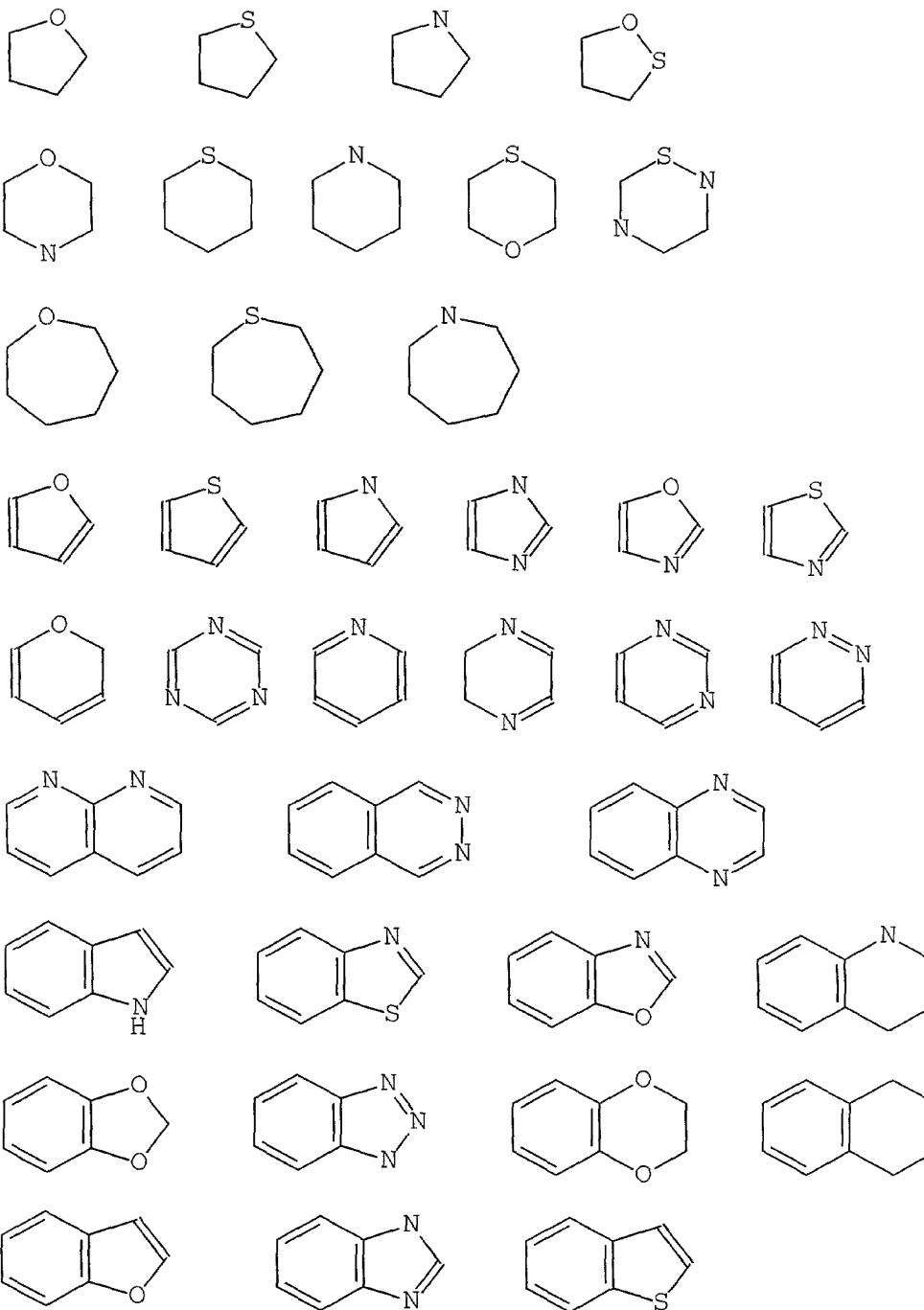
20 "Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring, multiple rings, or multiple condensed rings, and having at least one hetero atom such as nitrogen, oxygen, or sulfur within at

least one of the rings. "Heteroaryl" refers to a heterocycle in which at least one ring is aromatic. Any of the heterocyclic or heteroaryl groups can be unsubstituted or optionally substituted with one or more groups as defined above. Further, bi- or tri-cyclic heteroaryl moieties may comprise at least one ring which is either completely or partially saturated.

As one skilled in the art will appreciate, such heterocyclic moieties may exist in several isomeric forms, all of which are encompassed by the present invention. For example, a 1,3,5-triazine moiety is isomeric to a 1,2,4-triazine group. Such positional isomers are to be considered within the scope of the present invention. Likewise, the heterocyclic or heteroaryl groups can be bonded to other moieties in the compounds of the present invention. The point(s) of attachment to these other moieties is not to be construed as limiting on the scope of the invention. Thus, by way of example, a pyridyl moiety may be bound to other groups through the 2-, 3-, or 4-position of the pyridyl group. All such configurations are to be construed as within the scope of the present invention.

"Aralkyl" refers to alkyl or alkylene (alkenyl) chain which is substituted with aryl, heteroaryl, carbocycle or heterocycle, or alternatively one or more aryl, heteroaryl, carbocycle, or heterocycle(s) which is/are substituted with alkyl or alkenyl, i.e. 'Alkyl/alkylene which is substituted with Ar' or 'Ar which is substituted with alkyl/alkylene'.

Examples of heterocyclic or heteroaryl moieties included in the scope of the present invention may include, but are not limited to, the following:



"Halo" means at least one fluoro, chloro, bromo, or iodo moiety.

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compounds which possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. The salt, ester, or solvates can be formed with inorganic or organic acids such as acetate, adipate, alginate, aspartate, 5 benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride hydrobromide, 10 hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Base salt, ester, or solvates include ammonium 15 salts, alkali metal salts such as lithium, sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salt with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as: 1) lower alkyl halides, such as methyl, 20 ethyl, propyl, and butyl chloride, bromides and iodides; 2) dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; 3) long chain alkyls such as decyl, lauryl, myristyl and stearyl substituted with one or more halide such 25 as chloride, bromide and iodide; and 4) aryl or arylalkyl halides like benzyl and phenethyl bromide and others.

The compounds of this invention may possess at least one asymmetric center and thus can be produced as mixtures of stereoisomers or as individual enantiomers or diastereomers. 30 The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolution of the compound of formula (I). It is understood that the individual stereoisomers as well as mixtures (racemic and non-racemic) 35

of stereoisomers are encompassed by the scope of the present invention. The S-stereoisomer at atom 1 of formula I is a most preferred embodiment of the invention.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space.

"Isomers" are different compounds that have the same molecular formula and includes cyclic isomers such as (iso)indole and other isomeric forms of cyclic moieties.

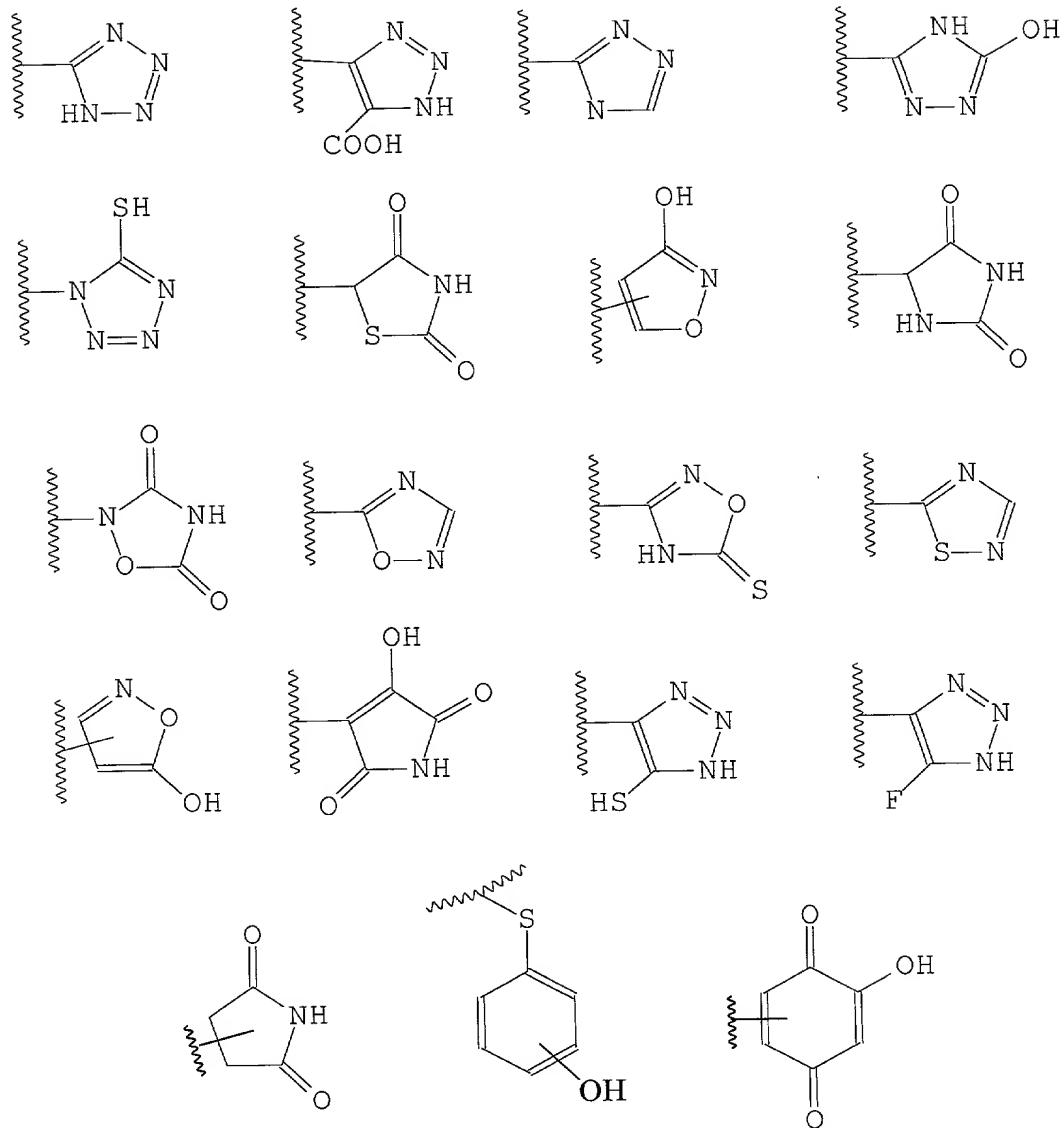
"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other.

"Diastereoisomers" are stereoisomers which are not mirror images of each other.

"Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

"Isosteres" are different compounds that have different molecular formulae but exhibit the same or similar properties. For example, tetrazole is an isostere of carboxylic acid because it mimics the properties of carboxylic acid even though they both have very different molecular formulae. Tetrazole is one of many possible isosteric replacements for carboxylic acid. Other carboxylic acid isosteres contemplated by the present invention include -COOH, -SO₃H, -SO₂HNR³, -PO₂(R³)₂, -CN, -PO₃(R³)₂, -OR³, -SR³, -NHCOR³, -N(R³)₂, -CON(R³)₂, -CONH(O)R³, -CONHNHSO₂R³, -COHNSO₂R³, and -CONR³CN.

In addition, carboxylic acid isosteres can include 5-7 membered carbocycles or heterocycles containing any combination of CH₂, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions. The following structures are non-limiting examples of preferred carbocyclic and heterocyclic isosteres contemplated by this invention.



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3 . The present invention contemplates that when chemical substituents are added to a carboxylic isostere then the inventive compound retains the properties of a carboxylic isostere.

The present invention contemplates that when a carboxylic isostere is optionally substituted with one or more moieties selected from R^3 , then the substitution cannot eliminate the carboxylic acid isosteric properties of the inventive compound. The present invention contemplates that the placement of one or more R^3 substituents upon a carbocyclic or heterocyclic carboxylic acid isostere shall not be at an atom(s) which maintains or is integral to the carboxylic acid isosteric properties of the inventive compound if such a substituent(s) would destroy the carboxylic acid isosteric properties of the inventive compound.

Other carboxylic acid isosteres not specifically exemplified or described in this specification are also contemplated by the present invention.

The system used in naming the compounds of the present invention is shown below, using a compound of formula I as an example.

A compound of the present invention, especially formula I, wherein n is 1, X is O, D is a bond, R_1 is 1,1-dimethylpropyl, and R_2 is -CN, is named (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarbonitrile.

"Alopecia" refers to deficient hair growth and partial or complete loss of hair, including without limitation androgenic alopecia (male pattern baldness), toxic alopecia, alopecia senilis, alopecia areata, alopecia pelada and trichotillomania. Alopecia results when the pilar cycle is disturbed. The most frequent phenomenon is a shortening of the hair growth or anagen phase due to cessation of cell proliferation. This results in an early onset of the catagen

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phase, and consequently a large number of hairs in the telogen phase during which the follicles are detached from the dermal papillae, and the hairs fall out. Alopecia has a number of etiologies, including genetic factors, aging, local and systemic diseases, febrile conditions, mental stresses, hormonal problems, and secondary effects of drugs.

"Pilar cycle" refers to the life cycle of hair follicles, and includes three phases:

- (1) the anagen phase, the period of active hair growth which, insofar as scalp hair is concerned, lasts about three to five years;
- (2) the catagen phase, the period when growth stops and the follicle atrophies which, insofar as scalp hair is concerned, lasts about one to two weeks; and
- (3) the telogen phase, the rest period when hair progressively separates and finally falls out which, insofar as scalp hair is concerned, lasts about three to four months.

Normally 80 to 90 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. In the telogen phase, hair is uniform in diameter with a slightly bulbous, non-pigmented root. By contrast, in the anagen phase, hair has a large colored bulb at its root.

The term "preventing neurodegeneration" as used herein includes the ability to inhibit or prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a new degenerative disease and for inhibiting or preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease when the compounds are given concurrently.

"Promoting hair growth" refers to maintaining, inducing, stimulating, accelerating, or revitalizing the germination of

hair.

The term "treatment" as used herein covers any treatment of a disease and/or condition in an animal, particularly a human, and includes:

5 (i) preventing a disease and/or condition from occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diagnosed as having it;

10 (ii) inhibiting the disease and/or condition, i.e., arresting its development; or

(iii) relieving the disease and/or condition, i.e., causing regression of the disease and/or condition.

"Treating alopecia" refers to:

15 (i) preventing alopecia in an animal which may be predisposed to alopecia; and/or

(ii) inhibiting, retarding or reducing alopecia; and/or

(iii) promoting hair growth; and/or

20 (iv) prolonging the anagen phase of the hair cycle; and/or

(v) converting vellus hair to growth as terminal hair. Terminal hair is coarse, pigmented, long hair in which the bulb of the hair follicle is seated deep in the dermis. Vellus hair, on the other hand, is fine, thin, non-pigmented short hair in which the hair bulb is located superficially in the dermis. As alopecia progresses, the hairs change from the terminal to the vellus type.

25 The term "neurotrophic" as used herein includes without limitation the ability to stimulate neuronal regeneration or growth and/or the ability to prevent or treat neurodegeneration.

30 The term "non-immunosuppressive" refers to the inability of the compounds of the present invention to trigger an immune response when compared to a control such as FK506 or cyclosporin A. Assays for determining immunosuppression are well known to those of ordinary skill in the art. Specific

non-limiting examples of well known assays include PMA and OKT3 assays wherein mitogens are used to stimulate proliferation of human peripheral blood lymphocytes (PBC). Compounds added to such assay systems are evaluated for their ability to inhibit such proliferation.

5 **Compounds of the Invention**

The present invention relates to the surprising discovery that carboxylic acid or carboxylic acid isostere compounds are neurotrophic and are able to treat alopecia. 10 Accordingly, a novel class of compounds are provided. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity.

Preferred compounds of the present invention contain carboxylic acid moieties and other isosteric replacements for carboxylic acid moieties, of which several examples are specified herein. Other isosteric replacements for carboxylic acid moieties, known to those skilled in the art of medicinal chemistry, are within the scope of the invention if not otherwise specified.

The neurotrophic compounds of this invention can be periodically administered to a patient undergoing treatment for neurological disorders or for other reasons in which it is desirable to stimulate neuronal regeneration and growth, such as in various peripheral neuropathic and neurological disorders relating to neurodegeneration. The compounds of this invention can also be administered to mammals other than humans for treatment of various mammalian neurological disorders.

30 The novel compounds of the present invention possess an excellent degree of neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and in the treatment of several neurological disorders known to be associated with neuronal

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degeneration and peripheral neuropathies. The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathic such as those caused by lead, dapsone, ticks, prophyria, or Gullain-Barré syndrome, Alzheimer's disease, and Parkinson's disease.

The above discussion relating to the utility and administration of the compounds of the present invention also applies to the pharmaceutical compositions of the present invention.

The term "pharmaceutically acceptable carrier" as used herein refers to any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbent, preservative, surfactant, colorant, flavorant, or sweetener.

For these purposes the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection or infusion techniques.

For oral administration, the compounds of the present invention may be provided in any suitable dosage form known in the art. For example, the compositions may be incorporated into tablets, powders, granules, beads, chewable lozenges, capsules, liquids, aqueous suspensions or

5 solutions, or similar dosage forms, using conventional equipment and techniques known in the art. Tablet dosage forms are preferred. Tablets may contain carriers such as lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules may contain diluents including lactose and dried corn starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient.

10 When preparing dosage forms incorporating the compositions of the invention, the compounds may also be blended with conventional excipients such as binders, including gelatin, pregelatinized starch, and the like; lubricants, such as hydrogenated vegetable oil, stearic acid, and the like; diluents, such as lactose, mannose, and sucrose; disintegrants, such as carboxymethylcellulose and sodium starch glycolate; suspending agents, such as povidone, polyvinyl alcohol, and the like; absorbents, such as silicon dioxide; preservatives, such as methylparaben, propylparaben, and sodium benzoate; surfactants, such as sodium lauryl sulfate, polysorbate 80, and the like; colorants such as F.D. & C. dyes and lakes; flavorants; and sweeteners.

15 Compositions and methods of the invention also may utilize controlled release technology. Thus, for example, the inventive compounds may be incorporated into a hydrophobic polymer matrix for controlled release over a period of days. Such controlled release films are well known to the art. Particularly preferred are transdermal delivery systems. Other examples of polymers commonly employed for this purpose that may be used in the present invention include nondegradable ethylene-vinyl acetate copolymer and degradable lactic acid-glycolic acid copolymers which may be used externally or internally. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly(vinylalcohol) also may be useful, but for shorter release cycles than the other polymer releases systems, such as those mentioned above.

To be effective therapeutically as central nervous system targets, the compounds of the present invention should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-
5 brain barrier can be effectively administered by an intraventricular route or other appropriate delivery system suitable for administration to the brain.

The compounds of the present invention may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions or suspensions in non-toxic parenterally-acceptable diluents or solvents, for example, as solutions in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending mediums. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

The compounds of this invention may also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

35 The compounds of this invention may also be administered

5 topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas.

10 For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively for the ophthalmic uses the compounds may be formulated in an ointment such as petrolatum.

15 For topical application to the skin, the compounds can be formulated in a suitable ointment containing the compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated in a suitable lotion or cream containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 20 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

25 Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation.

30 Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the 35

host treated and the particular mode of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The 5 considerations for determining the proper dose levels are well known in the art.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, 10 time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

To effectively treat alopecia or promote hair growth, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas. For these purposes, the compounds are preferably administered topically to the skin.

For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

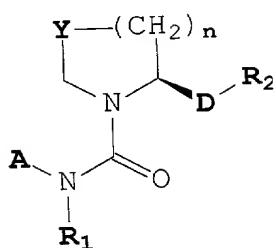
The compounds can be administered with other hair revitalizing agents. Specific dose levels for the other hair revitalizing agents will depend upon the factors previously stated and the effectiveness of the drug combination. Other 30 routes of administration known in the pharmaceutical art are

also contemplated by this invention.

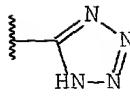
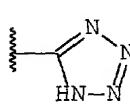
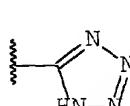
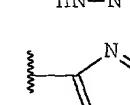
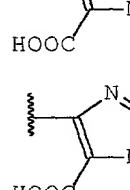
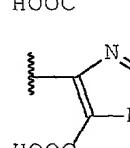
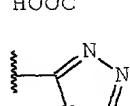
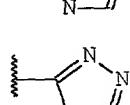
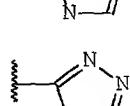
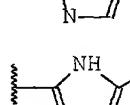
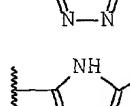
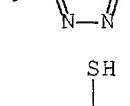
Specific embodiments of the inventive compounds are presented in Tables I, II, and III. The present invention contemplates employing the compounds of Tables I, II and III, below, for use in compositions and methods to prevent and/or treat a neurological disorder in an animal, and for use in compositions and methods to treat alopecia and promote hair growth in an animal, and all other uses suggested in this specification.

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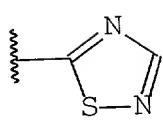
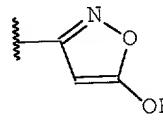
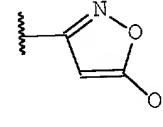
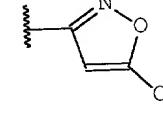
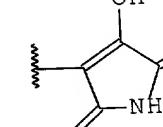
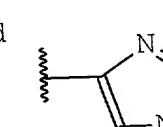
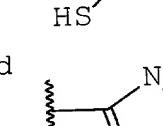
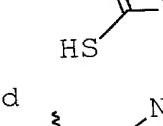
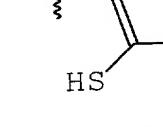
TABLE I



	No.	n	D	R2	A	Y	R1
10	1	1	bond	COOH	H	S	Benzyl
	2	1	bond	COOH	H	S	α -MethylBenzyl
	3	1	bond	COOH	H	S	4-MethylBenzyl
	4	1	bond	Tetrazole	H	S	Benzyl
	5	1	bond	SO ₃ H	H	O	α -MethylBenzyl
	6	1	CH ₂	COOH	H	O	4-MethylBenzyl
	7	1	bond	SO ₂ HNMe	H	O	Benzyl
	8	1	bond	CN	H	N	α -MethylBenzyl
	9	1	bond	PO ₃ H ₂	H	N	4-MethylBenzyl
	10	2	bond	COOH	H	N	Benzyl
20	11	2	bond	COOH	H	S	α -MethylBenzyl
	12	2	bond	COOH	H	S	4-MethylBenzyl
	13	2	bond	COOH	H	S	3,4,5-trimethoxyphenyl
	14	2	bond	COOH	H	S	Cyclohexyl
	15	2	bond	PO ₂ HET	H	O	i-propyl
	16	2	bond	PO ₃ HPropyl	H	O	ethyl
	17	2	bond	PO ₃ (Et) ₂	H	N	Methyl
	18	2	bond	OMe	H	S	tert-butyl
	19	2	bond	OEt	H	S	n-pentyl
	20	2	bond	OPropyl	H	S	n-hexyl
30	21	1	bond	OButyl	H	O	Cyclohexyl
	22	1	bond	OPentyl	H	N	cyclopentyl
	23	1	bond	OHexyl	H	S	n-heptyl
	24	1	bond	SMe	H	S	n-octyl
	25	1	bond	SET	H	O	n-nonyl
	26	2	bond	SPropyl	H	N	2-indolyl
	27	2	bond	SButyl	H	O	2-furyl
	28	2	bond	NHCOMe	H	S	2-thiazolyl
	29	2	bond	NHCOEt	H	S	2-thienyl
	30	1	CH ₂	N(Me) ₂	H	N	2-pyridyl
40	31	1	(CH ₂) ₂	N(Me)Et	H	S	1,1-dimethylpropyl
	32	1	(CH ₂) ₃	CON(Me) ₂	H	O	1,1-dimethylpropyl
	33	1	(CH ₂) ₄	CONHMe	H	N	1,1-dimethylpropyl
	34	1	(CH ₂) ₅	CONHET	H	S	1,1-dimethylpropyl
	35	1	(CH ₂) ₆	CONHPropyl	H	S	1,1-dimethylpropyl

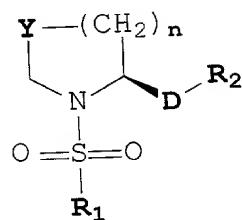
No.	n	D	R2	A	Y	R1	
36	1	bond		CH ₂	S	Hydrogen	
5	37	1	bond		(CH ₂) ₂	S	Cyclohexyl
38	1	bond		(CH ₂) ₃	S	Adamantyl	
39	1	bond		(CH ₂) ₄	S	Pentafluorobenzyl	
40	1	bond		(CH ₂) ₅	O	3,4,5-trimethoxyphenyl	
41	1	CH ₂		(CH ₂) ₆	O	Phenyl	
10	42	1	bond		CH ₂	O	2-furyl
43	1	bond		(CH ₂) ₂	N	2-thienyl	
44	1	bond		(CH ₂) ₃	N	2-thiazolyl	
45	2	bond		(CH ₂) ₄	N	1,1-dimethylbutyl	
46	2	bond		(CH ₂) ₅	S	Hydrogen	
15	47	2	bond		(CH ₂) ₆	S	Hydrogen

No.	n	D	R2	A	Y	R1
5	48	2	bond		CH ₂	S 3,4,5-trimethoxyphenyl
	49	2	bond		(CH ₂) ₂	S 3,4,5-trimethoxyphenyl
	50	2	bond		(CH ₂) ₃	O Cyclohexyl
	51	2	bond		(CH ₂) ₄	O Cyclohexyl
	52	2	bond		(CH ₂) ₅	N Adamantyl
10	53	2	bond		(CH ₂) ₆	S Adamantyl
	54	2	bond		CH ₂	S Pentafluorobenzyl
	55	2	bond		(CH ₂) ₂	S Pentafluorobenzyl
	56	1	bond		(CH ₂) ₃	O Phenyl

No.	n	D	R2	A	Y	R1	
57	1	bond		(CH ₂) ₄ N		Phenyl	
5	58	1	bond		(CH ₂) ₅ S	2-furyl	
59	1	bond		(CH ₂) ₆ S		2-furyl	
60	1	bond		CH ₂	O	2-thienyl	
61	2	bond		(CH ₂) ₂ N		2-thienyl	
62	2	bond		(CH ₂) ₃ O		2-thiazolyl	
10	63	2	bond		(CH ₂) ₄ S		2-thiazolyl
64	2	bond		(CH ₂) ₅ S		1,1-dimethylbutyl	
65	1	CH ₂		(CH ₂) ₆ N		1,1-dimethylbutyl	

No.	n	D	R2	A	Y	R1
66	1	$(\text{CH}_2)_2$		CH_2	S	1,1-dimethylpropyl
5	67	1	$(\text{CH}_2)_3$		$(\text{CH}_2)_2 \text{ O}$	1,1-dimethylpropyl
68	1	$(\text{CH}_2)_4$		$(\text{CH}_2)_3 \text{ N}$	1,1-dimethylpropyl	
69	1	$(\text{CH}_2)_5$		$(\text{CH}_2)_4 \text{ S}$	1,1-dimethylpropyl	
70	1	$(\text{CH}_2)_6$		$(\text{CH}_2)_5 \text{ S}$	1,1-dimethylpropyl	

TABLE II

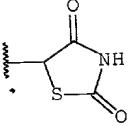
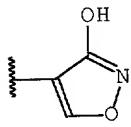
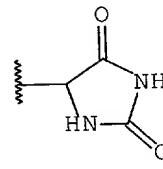
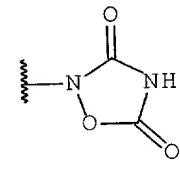
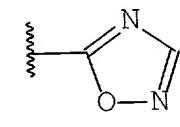
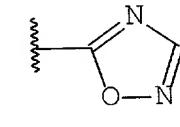
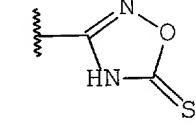
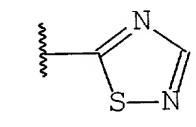
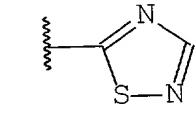
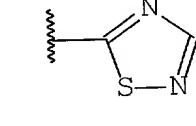


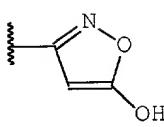
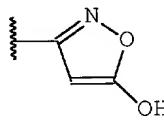
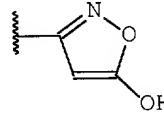
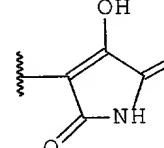
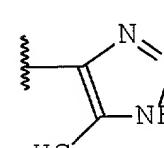
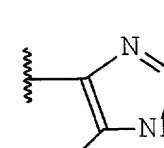
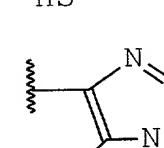
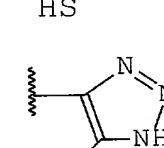
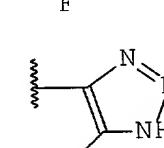
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No.	n	D	R2	Y	R1	
15	71	1	bond	CONH(O)Me	S	Benzyl
	72	1	bond	CONH(O)Et	S	α -Methylphenyl
	73	1	bond	CONH(O)Propyl	S	4-Methylphenyl
	74	2	bond	COOH	S	Benzyl
	75	2	bond	COOH	O	α -Methylphenyl
	76	2	bond	COOH	O	4-Methylphenyl
	77	1	CH ₂	COOH	N	benzyl
	78	1	(CH ₂) ₂	COOH	N	benzyl
	79	1	(CH ₂) ₃	COOH	N	benzyl
	80	1	(CH ₂) ₄	COOH	S	benzyl
20	81	1	(CH ₂) ₅	COOH	S	benzyl
	82	1	(CH ₂) ₆	COOH	S	benzyl
	83	1	(CH ₂) ₇	COOH	O	benzyl
	84	1	(CH ₂) ₈	COOH	O	benzyl
	85	1	(CH ₂) ₉	COOH	O	benzyl
	86	1	(CH ₂) ₁₀	COOH	N	benzyl
	87	1	C ₂ H ₅	COOH	N	benzyl
	88	1	2-OH, Et	COOH	N	benzyl
	89	1	2butylene	COOH	S	benzyl
	90	1	i-Pro	COOH	S	benzyl
25	91	1	tert-Bu	COOH	S	benzyl
	92	1	2-nitro	COOH	S	benzyl
	93	3	(CH ₂) ₂	CN	S	benzyl
	94	1	(CH ₂) ₃	CN	S	benzyl
	95	3	bond	CONHNHSO ₂ Me	N	Benzyl
	96	3	bond	CONHNHSO ₂ Et	N	α -Methylphenyl
	97	3	bond	CONHSO ₂ Me	N	4-Methylphenyl
	98	2	bond	CONHNHSO ₂ Et	N	Phenyl
	99	2	bond	CON(Me)CN	O	α -Methylphenyl
	100	2	bond	CON(Et)CN	O	4-Methylphenyl
30	101	1	(CH ₂) ₂	COOH	O	methyl
	102	1	(CH ₂) ₃	COOH	O	ethyl
	103	1	(CH ₂) ₄	COOH	N	n-propyl
	104	1	(CH ₂) ₅	COOH	N	t-butyl
	105	1	(CH ₂) ₆	COOH	N	Pentyl
	106	1	(CH ₂) ₇	COOH	S	Hexyl
	107	1	(CH ₂) ₈	COOH	S	Septyl
	108	1	(CH ₂) ₉	COOH	S	Octyl
	109	1	(CH ₂) ₁₀	COOH	S	Nonyl
Hexyl						
35	93	3	(CH ₂) ₂	CN	S	benzyl
	94	1	(CH ₂) ₃	CN	S	benzyl
	95	3	bond	CONHNHSO ₂ Me	N	Benzyl
	96	3	bond	CONHNHSO ₂ Et	N	α -Methylphenyl
	97	3	bond	CONHSO ₂ Me	N	4-Methylphenyl
	98	2	bond	CONHNHSO ₂ Et	N	Phenyl
	99	2	bond	CON(Me)CN	O	α -Methylphenyl
	100	2	bond	CON(Et)CN	O	4-Methylphenyl
	101	1	(CH ₂) ₂	COOH	O	methyl
	102	1	(CH ₂) ₃	COOH	O	ethyl
40	103	1	(CH ₂) ₄	COOH	N	n-propyl
	104	1	(CH ₂) ₅	COOH	N	t-butyl
	105	1	(CH ₂) ₆	COOH	N	Pentyl
	106	1	(CH ₂) ₇	COOH	S	Hexyl
	107	1	(CH ₂) ₈	COOH	S	Septyl
	108	1	(CH ₂) ₉	COOH	S	Octyl
	109	1	(CH ₂) ₁₀	COOH	S	Nonyl
45	93	3	(CH ₂) ₂	CN	S	benzyl
	94	1	(CH ₂) ₃	CN	S	benzyl
	95	3	bond	CONHNHSO ₂ Me	N	Benzyl
	96	3	bond	CONHNHSO ₂ Et	N	α -Methylphenyl
	97	3	bond	CONHSO ₂ Me	N	4-Methylphenyl
	98	2	bond	CONHNHSO ₂ Et	N	Phenyl
	99	2	bond	CON(Me)CN	O	α -Methylphenyl
	100	2	bond	CON(Et)CN	O	4-Methylphenyl
	101	1	(CH ₂) ₂	COOH	O	methyl
	102	1	(CH ₂) ₃	COOH	O	ethyl
50	103	1	(CH ₂) ₄	COOH	N	n-propyl
	104	1	(CH ₂) ₅	COOH	N	t-butyl
	105	1	(CH ₂) ₆	COOH	N	Pentyl
	106	1	(CH ₂) ₇	COOH	S	Hexyl
	107	1	(CH ₂) ₈	COOH	S	Septyl
	108	1	(CH ₂) ₉	COOH	S	Octyl
	109	1	(CH ₂) ₁₀	COOH	S	Nonyl

No.	n	D	R2	Y	R1	
110	1	C_2H_2	COOH	S	Cyclohexyl	
111	1	bond		S	Hydrogen	
5	112	1	bond		S	Cyclohexyl
113	1	bond		S	Adamantyl	
114	1	bond		S	Pentafluorobenzyl	
115	1	bond		O	3, 4, 5-trimethoxyphenyl	
10	116	1	CH_2		O	Phenyl
117	1	bond		O	2-furyl	
118	1	bond		N	2-thienyl	
119	1	bond		N	2-thiazolyl	
120	2	bond		N	1,1-dimethylbutyl	
121	2	bond		S	Hydrogen	
15	122	2	bond		S	Hydrogen

No.	n	D	R2	Y	R1	
123	2	bond		S	3, 4, 5-trimethoxyphenyl	
124	2	bond		S	3, 4, 5-trimethoxyphenyl	
5	125	2	bond		O	Cyclohexyl
	126	2	bond		O	Cyclohexyl
	127	2	bond		N	Adamantyl
	128	2	bond		S	Adamantyl
	129	2	bond		S	Pentafluorobenzyl
10	130	2	bond		S	Pentafluorobenzyl
	131	1	bond		O	Phenyl
	132	1	bond		N	Phenyl

No.	n	D	R2	Y	R1	
133	1	bond		S	2-furyl	
134	1	bond		S	2-furyl	
5	135	1	bond		O	2-thienyl
136	2	bond		N	2-thienyl	
137	2	bond		O	2-thiazolyl	
138	2	bond		S	2-thiazolyl	
139	2	bond		S	1,1-dimethylbutyl	
10	140	1	CH ₂		N	1,1-dimethylbutyl
141	1	(CH ₂) ₂		S	1,1-dimethylpropyl	

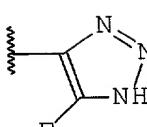
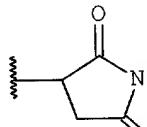
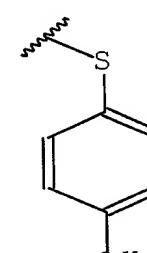
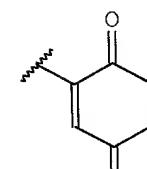
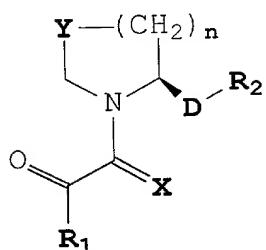
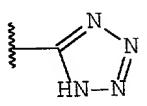
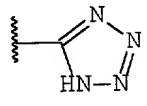
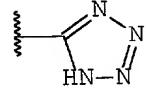
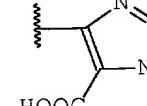
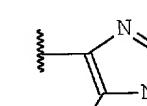
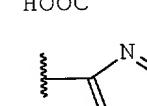
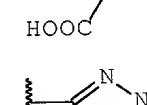
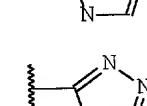
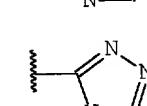
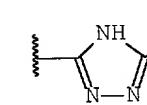
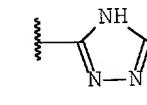
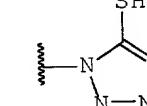
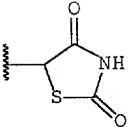
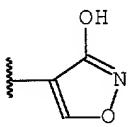
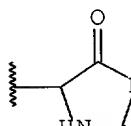
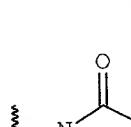
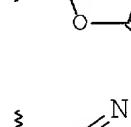
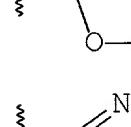
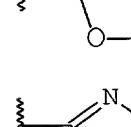
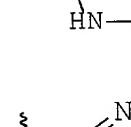
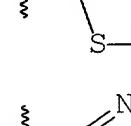
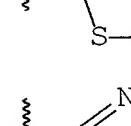
No.	n	D	R2	Y	R1	
142	1	$(\text{CH}_2)_3$		O	1,1-dimethylpropyl	
143	1	$(\text{CH}_2)_4$		N	1,1-dimethylpropyl	
5	144	1	$(\text{CH}_2)_5$		S	1,1-dimethylpropyl
145	1	$(\text{CH}_2)_6$		S	1,1-dimethylpropyl	

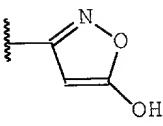
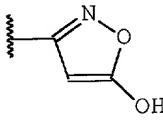
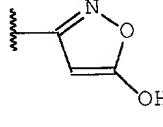
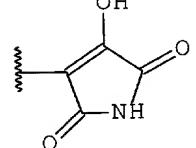
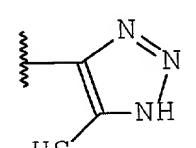
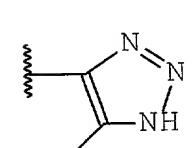
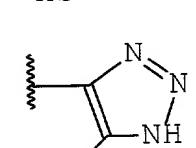
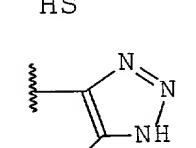
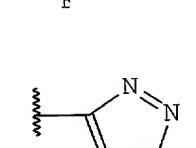
TABLE III



5	No.	n	X	D	R2	Y	R1
	146	1	O	bond	CONH(O)Me	S	Benzyl
	147	1	O	bond	CONH(O)Et	S	α -Methylphenyl
	148	1	O	bond	CONH(O)Propyl	S	4-Methylphenyl
10	149	2	O	bond	COOH	S	Benzyl
	150	2	O	bond	COOH	O	α -Methylphenyl
	151	2	O	bond	COOH	O	4-Methylphenyl
	152	1	O	CH ₂	COOH	N	benzyl
	153	1	O	(CH ₂) ₂	COOH	N	benzyl
	154	1	O	(CH ₂) ₃	COOH	N	benzyl
	155	1	O	(CH ₂) ₄	COOH	S	benzyl
	156	1	O	(CH ₂) ₅	COOH	S	benzyl
	157	1	O	(CH ₂) ₆	COOH	S	benzyl
	158	1	O	(CH ₂) ₇	COOH	S	benzyl
	159	1	O	(CH ₂) ₈	COOH	O	benzyl
	160	1	O	(CH ₂) ₉	COOH	O	benzyl
	161	1	O	(CH ₂) ₁₀	COOH	O	benzyl
	162	1	O	C ₂ H ₅	COOH	N	benzyl
	163	1	O	2-OH, Et	COOH	N	benzyl
	164	1	O	2butylene	COOH	S	benzyl
	165	1	O	i-Pro	COOH	S	benzyl
	166	1	S	tert-Bu	COOH	S	benzyl
	167	1	S	2-nitro Hexyl	COOH	S	benzyl
30	168	3	S	(CH ₂) ₂	CN	S	benzyl
	169	1	S	(CH ₂) ₃	CN	S	benzyl
	170	3	S	bond	CONHNHSO ₂ Me	N	Benzyl
	171	3	S	bond	CONHNHSO ₂ Et	N	α -Methylphenyl
	172	3	S	bond	CONHSO ₂ Me	N	4-Methylphenyl
	173	2	S	bond	CONHNHSO ₂ Et	N	Phenyl
	174	2	S	bond	CON(Me)CN	O	α -Methylphenyl
	175	2	S	bond	CON(Et)CN	O	4-Methylphenyl
	176	1	S	(CH ₂) ₂	COOH	O	methyl
	177	1	S	(CH ₂) ₃	COOH	O	ethyl
40	178	1	S	(CH ₂) ₄	COOH	N	n-propyl
	179	1	S	(CH ₂) ₅	COOH	N	t-butyl
	180	1	S	(CH ₂) ₆	COOH	N	Pentyl
	181	1	S	(CH ₂) ₇	COOH	S	Hexyl
	182	1	S	(CH ₂) ₈	COOH	S	Septyl
45	183	1	S	(CH ₂) ₉	COOH	S	Octyl

	No.	n	X	D	R2	Y	R1
5	184	1	S	$(\text{CH}_2)_{10}$	COOH	S	Nonyl
	185	1	S	C_2H_2	COOH	S	Cyclohexyl
	186	1	O	bond		S	Hydrogen
	187	1	O	bond		S	Cyclohexyl
	188	1	O	bond		S	Adamantyl
	189	1	O	bond		S	Pentafluorobenzyl
	190	1	O	bond		O	3,4,5-trimethoxyphenyl
10	191	1	O	CH_2		O	Phenyl
	192	1	O	bond		O	2-furyl
	193	1	O	bond		N	2-thienyl
	194	1	O	bond		N	2-thiazolyl
	195	2	O	bond		N	1,1-dimethylbutyl
	196	2	O	bond		S	Hydrogen
	197	2	O	bond		S	Hydrogen

No.	n	X	D	R2	Y	R1	
198	2	O	bond		S	3,4,5-trimethoxyphenyl	
5	199	2	O	bond		S	3,4,5-trimethoxyphenyl
200	2	O	bond		O	Cyclohexyl	
201	2	O	bond		O	Cyclohexyl	
202	2	O	bond		N	Adamantyl	
203	2	S	bond		S	Adamantyl	
10	204	2	S	bond		S	Pentafluorobenzyl
205	2	S	bond		S	Pentafluorobenzyl	
206	1	S	bond		O	Phenyl	
207	1	S	bond		N	Phenyl	

No.	n	X	D	R2	Y	R1	
208	1	S	bond		S	2-furyl	
5	209	1	S	bond		S	2-furyl
210	1	S	bond		O	2-thienyl	
211	2	S	bond		N	2-thienyl	
212	2	S	bond		O	2-thiazolyl	
213	2	S	bond		S	2-thiazolyl	
10	214	2	S	bond		S	1,1-dimethylbutyl
215	1	S	CH ₂		N	1,1-dimethylbutyl	
216	1	S	(CH ₂) ₂		S	1,1-dimethylpropyl	

No.	n	X	D	R2	Y	R1	
217	1	S	$(CH_2)_3$		O	1,1-dimethylpropyl	
5	218	1	S	$(CH_2)_4$		N	1,1-dimethylpropyl
219	1	S	$(CH_2)_5$		S	1,1-dimethylpropyl	
220	1	S	$(CH_2)_6$		S	1,1-dimethylpropyl	

10

Compounds 221-440 are also exemplified in the present invention, and are defined as where Y is located at the 3-position of the heterocyclic ring for compounds 1-220, and n, 15 A, D, Y, X, R₁, and R₂ remain the same as defined for compounds 1-220 in Tables I, II, and III.

Exemplary compound 441 is defined where S is located at the 3-position of the heterocyclic ring (3-thiazolidine), n is 1, R₁ is 1,1-dimethylpropyl, D is a bond, R₂ is COOH.

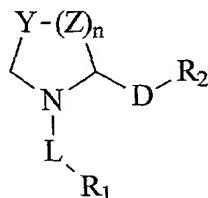
20 Exemplary compound 442 is defined where O is located at the 2-position of the heterocyclic ring (2-oxopentanoyl), n is 1, R₁ is 1,1-dimethylpropyl, D is a bond, R₂ is COOH (i.e. 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylic acid).

The present invention also contemplates other ring locations for the heteroatoms O, N, and S in neurotrophic heterocyclic compounds. Also contemplated by the present invention are neurotrophic heterocycles containing 3 or more heteroatoms chosen independently from O, N, and S.

Additional claimed or comparative carboxylic acids and isosteres of N-heterocyclic compounds which also show the remarkable neurotrophic and hair growth effects of the present invention are shown below in Table IV:

10

TABLE IV



Cpd.	n	D	R ₂	L	R ₁
A	1	bond	COOH	SO ₂	Benzyl
B	1	bond	CONH ₂	SO ₂	Benzyl
C	1	bond	-CN	SO ₂	Benzyl
D	1	bond	tetrazole	SO ₂	Benzyl
E	1	CH ₂	-OH	SO ₂	Benzyl
F	1	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl
G	2	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl
H	1	CH ₂	OH	1,2-dioxoethyl	1,1-dimethylpropyl
I	1	bond	tetrazole	1,2-dioxoethyl	1,1-dimethylpropyl
J	1	bond	-CN	1,2-dioxoethyl	1,1-dimethylpropyl
K	2	bond	CONH ₂	1,2-dioxoethyl	1,1-dimethylpropyl
where Y and Z are both carbon for compounds A-K,					
L	1	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl
M	1	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl

where Z is S for compound L or where Y is S for compound M.

Pharmaceutical Compositions of the Present Invention

The present invention relates to a pharmaceutical composition comprising:

(i) an effective amount of a carboxylic acid or

carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring; and

(ii) a pharmaceutically acceptable carrier.

5

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring for treating neurodegenerative diseases, neurological disorders, and nerve damage, or promoting nerve growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

15

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring for treating alopecia or promoting hair growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

25

The compounds can be administered with other neurotrophic agents such as neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3 and neurotropin 4/5. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

35

Methods of the Present Invention

The present invention relates to the use of any of the compounds seen in Tables I, II, III, and IV, any of the other compounds described above, and other compounds not specifically mentioned or described herein, in the preparation of a medicament for the treatment of a disease such as peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis. The present invention also relates to the use of carboxylic acid and carboxylic acid isostere compounds for treating the above-mentioned neuropathies, neurological disorders, and neurological damage.

The present invention also relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring. The present invention also relates to using the inventive compounds and compositions in the preparation of a medicament for the treatment of alopecia or promoting hair growth in an animal.

The inventive method is particularly useful for treating male pattern alopecia, alopecia senilis, alopecia areata, alopecia resulting from skin lesions or tumors, alopecia resulting from cancer therapy such as chemotherapy and radiation, and alopecia resulting from systematic disorders such as nutritional disorders and internal secretion disorders.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease or disorder being treated and form of administration.

MPTP Model of Parkinson's Disease in Mice

MPTP lesioning of dopaminergic neurons in mice is used as an animal model of Parkinson's Disease. Four week old male CD1 white mice are dosed i.p. with 30 mg/kg of MPTP for 5 days. 5 Test compounds (4 mg/kg), or vehicle, are administered s.c. along with the MPTP for 5 days, as well as for an additional 5 days following cessation of MPTP treatment. At 18 days following MPTP treatment, the animals are sacrificed and the striata dissected and perfusion-fixed. Immunostaining is 10 performed on saggital and coronal brain sections using anti-tyrosine hydroxylase 1 g to quantitate survival and recovery of dopaminergic neurons. In animals treated with MPTP and vehicle, a substantial loss of functional dopaminergic terminals is observed as compared to non-lesioned animals. Lesioned animals 15 receiving test compounds show a significant recovery of TH-stained dopaminergic neurons. This model presents quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving the compounds of the present invention.

Table V presents the percent recovery of dopaminergic neurons in the first (concurrent dosing) paradigm in animals receiving (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-3-thiazolidine-2-carboxylic acid as well as claimed or comparative compounds 443-448.

Table V, below, shows the remarkable neuroregenerative effects of carboxylic acid or carboxylic acid isostere related compounds illustrating the neurotrophic capability of carboxylic acid isosteres as a class showing that lesioned animals receiving the carboxylic acid or carboxylic acid isostere compounds provide a remarkable recovery of TH-stained dopaminergic neurons.

Table V - MPTP Neurodegenerative Model

	% Recovery
	Compound A
5	24.4 %
	Cmpds B-E
	ND
10	Compound F
	26.7 %
	Compound G
	ND
	Compound H
	23.2 %
	Compound I
	19.6 %
	Compound J
	34.1 %
15	Compound K
	46.5 %
	Compound L
	14.0 %
20	Compound M
	ND

Percent striatal innervation density was quantitated in brain sections with an anti-tyrosine hydroxylase immunoglobulin, which is indicative of functional dopaminergic neurons. The striatal innervation density of 23% for animals pretreated with only a vehicle and administered a vehicle orally during treatment, is indicative of normal non-lesioned striatal tissue. Striatal innervation density is reduced to 5% for animals pretreated with MPTP and administered a vehicle orally during treatment, and is indicative of MPTP-induced lesioning. Surprisingly, striatal innervation density is increased 8-13% for animals pretreated with MPTP and administered 0.4 mg/kg, orally during treatment, indicating substantial neuronal regeneration after induction of MPTP-derived lesions.

In Vivo Hair Generation Test With C57 Black 6 Mice

C57 black 6 mice are used to demonstrate the hair revitalizing properties of the ureas and carbamates of N-heterocyclic carboxylic acids or carboxylic acid isosteres. Referring now to FIGS. 1 and 2 of the drawings, C57 black 6 mice, approximately 7 weeks old, had an area of about 2 inches by 2 inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion

to the underlaying dermal layers. The animals were in anagen growth phase, as indicated by the pinkish color of the skin. Referring now to FIG. 2, four animals per group were treated by topical administration with 20% propylene glycol vehicle (FIG. 2), or related compounds dissolved in the vehicle. The animals were treated with vehicle or N-heterocyclic carboxylic acids or isosteres every 48 hours (3 applications total over the course of 5 days) and the hair growth was allowed to proceed for 6 weeks. Hair growth was quantitated by the percent of shaved area covered by new hair growth during this time period.

FIG. 2 shows that animals treated with vehicle exhibited only a small amount of hair growth in patches or tufts, with less than 3% of the shaved area covered with new growth.

In contrast, FIG. 3 shows that animals treated for 2 weeks with the N-heterocyclic carboxylic acid compounds i.e. compound F, compound G, and compound K exhibited dramatic hair growth, covering greater than 25% of the shaved area in all animals for two of the compounds.

FIG. 3 shows the relative hair growth on shaven C57 black 6 mice 14 days after being treated with N-heterocyclic carboxylic acids or carboxylic acid isosteres. The mice had a 2 x 2 inch region on their backside shaved to remove all hair. Care was taken not to nick or cause abrasion to the underlying dermal layers. Compounds at a concentration of 1 μ mole per milliliter were carefully applied to the shaved area of the mice (5 mice per group) three times per week. Hair growth was evaluated 14 days after initiation of drug treatment. The relative scale for assessing hair growth is as follows:

- 0 = no growth;
- 1 = beginning of growth in small tufts;
- 2 = hair growth covering over <25% of shaved area;
- 3 = hair growth covering over >25% of shaved area, but less than 50% of shaved area;

4 = hair growth covering over >50% of shaved area, but less than 75% of shaved area;
5 = complete hair growth of shaved area.

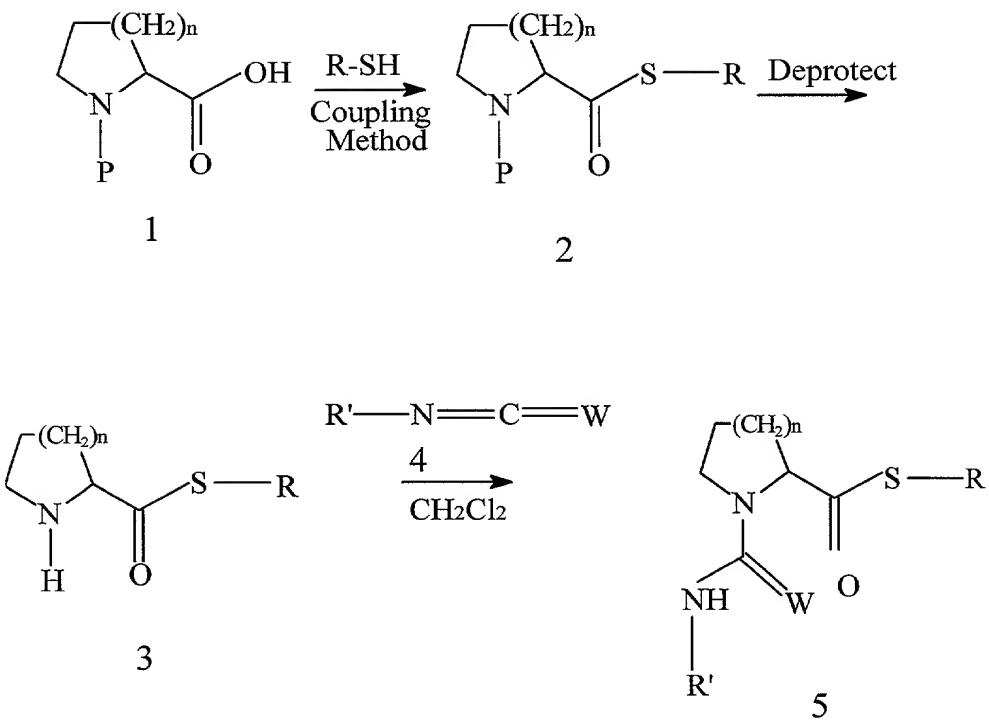
5 The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All polymer molecular weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.
10

SYNTHETIC SCHEMES

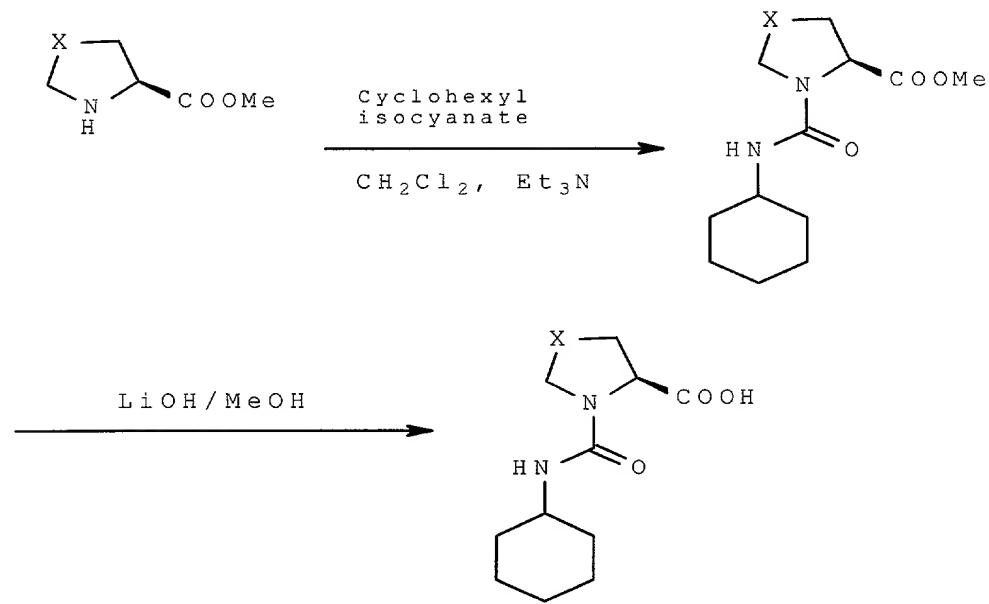
15 The novel compounds of this invention may be readily prepared by standard techniques of organic chemistry, utilizing the general synthetic pathways depicted below for diketo derivatives, sulfonamide derivatives, and urea or carbamate derivatives.

20 Cyclic amino acids **1** protected by suitable blocking groups P on the amino acid nitrogen may be reacted with thiols RSH to generate thioesters **2**. After removal of the protecting group, the free amine **3** may be reacted with a variety of isocyanates or isothiocyanates to provide final ureas or thioureas, respectively.

SCHEME I



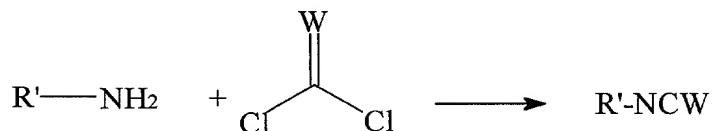
5
Another scheme for preparing ureas or carbamates
is set forth below.



SCHEME II

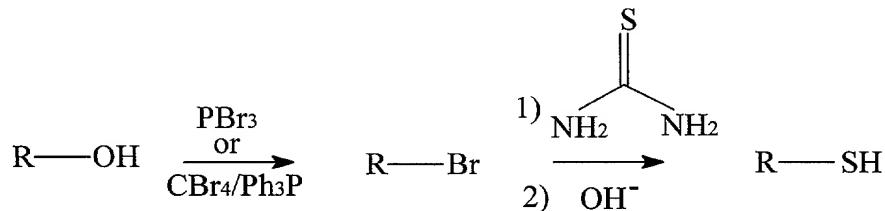
Isocyanates ($R'NCO$) or isothiocyanates ($R'NCS$) **4** may be conveniently prepared from the corresponding readily available amines by reaction with phosgene or thiophosgene, as depicted below.

5



SCHEME III

Thiols $R—SH$ may be conveniently prepared from the corresponding readily available alcohols or halides via a two step replacement of halide by sulfur, as described below. Halides may be reacted with thiourea, and the corresponding alkyl thiouronium salts hydrolyzed to provide thiols RSH . If alcohols are used as the starting materials, they may be first converted to the corresponding halides by standard methods.

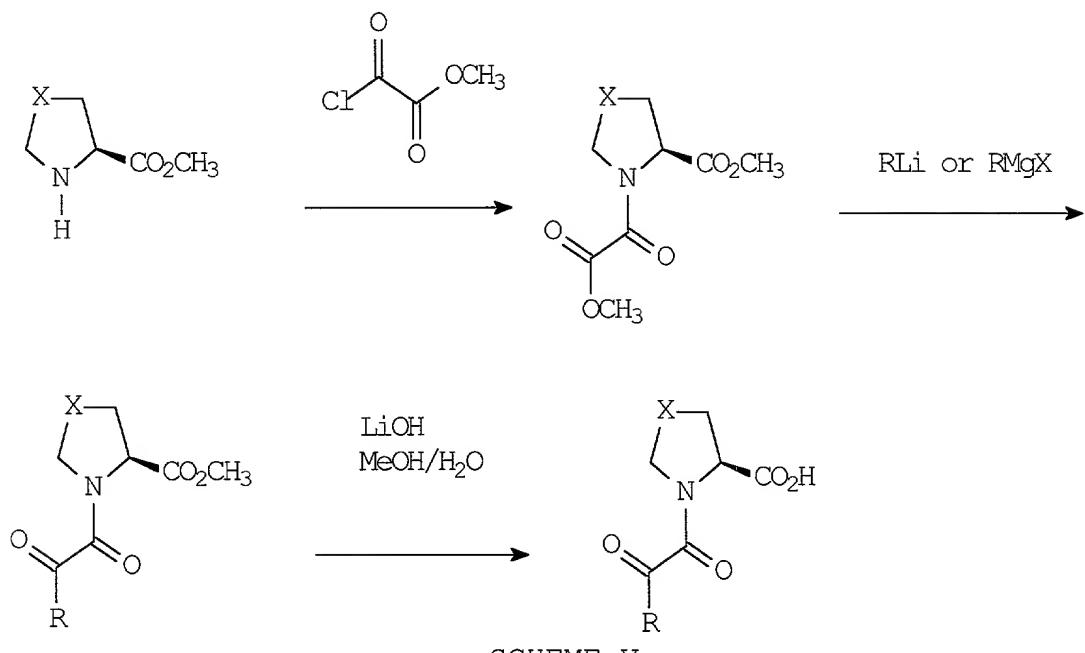


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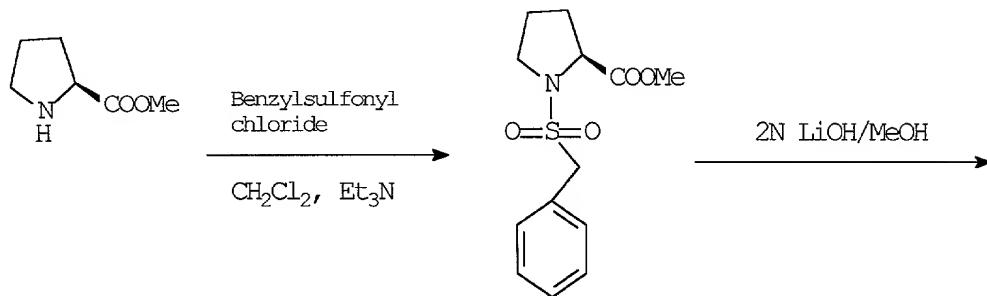
SCHEME IV

25 N-glyoxylproline derivatives may be prepared by reacting L-proline methyl ester with methyl oxalyl chloride as shown below. The resulting oxamates may be reacted with a variety of carbon nucleophiles to obtain compounds of the present invention or useful for preparing

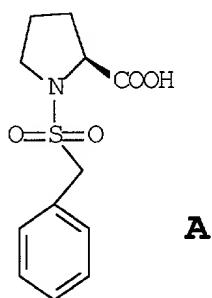
compounds of the present invention.



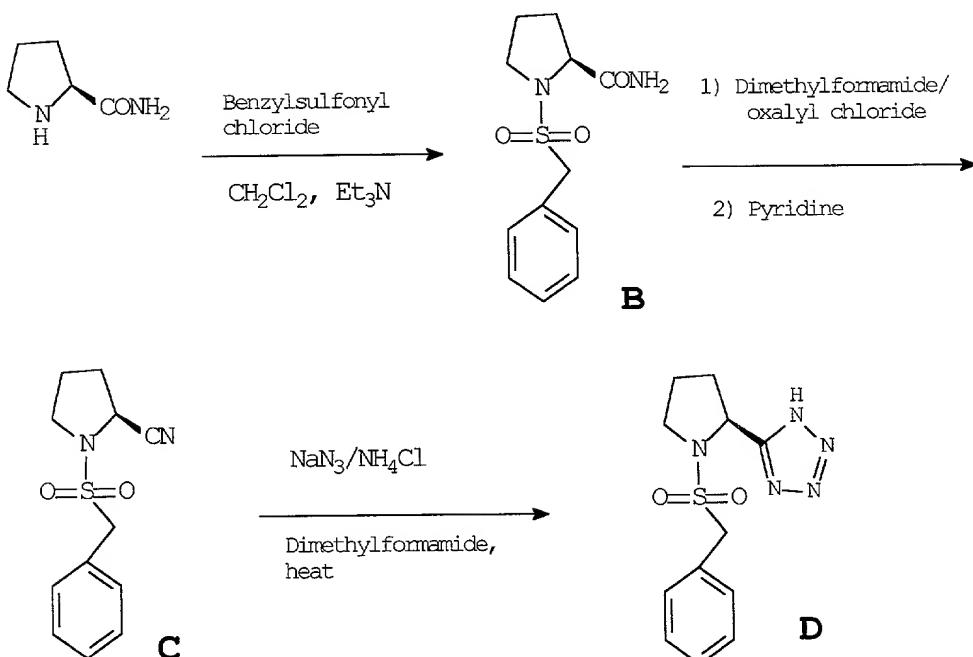
5 Synthetic schemes for preparing sulfonamide derivatives are known in the art and compounds of the present invention may be synthesized using schemes such as are set forth



10 below.



SCHEME VI



SCHEME VII

5 **Examples**

10 The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise specified, all percentages are based on 100% by weight of the final compound.

15 **EXAMPLE 1**

Synthesis of 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylic acid (4) (Compound 190).

20 Methyl 1,3-oxazolidine-4-carboxylate (1) was synthesized according to the procedure found in *J. Med. Chem.*, 1990, 33, 1459-1469.

25 Methyl 2-[4-(methoxycarbonyl)(1,3-oxazolidin-3-yl)]-2-oxoacetate (2). To an ice cooled solution of methyl 1,3-oxazolidine-4-carboxylate (1) (0.65 g, 4.98 mM) were added triethylamine (0.76 ml, 5.45 mM) and methyl oxalyl

chloride (0.5 ml, 5.45 mM). This mixture was stirred at 0°C for 2 hours. After this time the mixture was washed with water, then brine, dried with anhydrous magnesium sulfate, filtered and evaporated. The resulting pale yellow oil was flash chromatographed eluting with 30% EtOAc/hexane, 50% EtOAc/hexane, and finally 75% EtOAc/hexane. A clear oil of product (0.52 g, 48%) was obtained. Anal. $(C_8H_{11}NO_6)C, H, N.$

¹H NMR (CDCl₃, 400 MHz): d (2 rotamers 1:1) 3.78 (s, 1.5H); 3.79 (s, 1.5H); 3.87 (s, 1.5H); 3.91 (s, 1.5H); 4.14-4.36 (m, 2H); 4.70 (dd, 0.5H, J=4.1, 6.8); 5.08 (dd, 0.5H, J=3.1, 6.7); 5.10 (d, 0.5H, J=5.9); 5.27 (d, 0.5H, J=5.8); 5.36 (dd, 1H, J=5.3, 17.8).

15 Methyl 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylate (3).

To a solution of methyl 2-[4-(methoxycarbonyl)(1,3-oxazolidin-3-yl)]-2-oxoacetate (2) (0.84 g, 3.87 mM) in THF (50 ml) cooled to -78°C was added 1,1-dimethylpropylmagnesium chloride (1M in THF, 8ml, 8 mM). After 3 hrs. at -78°C the mixture was quenched with saturated NH₄Cl (50 ml) and extracted with ethyl acetate (100 ml). The organic layer separated, washed with brine (100 ml), dried with anhydrous magnesium sulfate, filtered and evaporated. The resulting pale yellow oil was flash chromatographed eluting with 20% EtOAc/hexane. A clear oil (3) (0.61 g, 61%) was obtained.

¹H NMR (CDCl₃, 400 MHz): d 0.85 (t, 3H, J=7.5); 1.25 (s, 3H); 1.26 (s, 3H); 1.67-1.94 (m, 2H); 3.79 (s, 3H); 4.12-4.31 (m, 2H); 4.64 (dd, 1H, J=4.1, 6.8); 5.04 (dd, 2H, J=4.9, 9.4).

3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylic acid (4).

35 Dissolved methyl 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-

oxazolidine-4-carboxylate (3) (0.6 g, 2.33 mM) in MeOH (25 ml) and added LiOH (1M in water, 10 ml, 10 mM). Stirred this mixture overnight at room temperature. Evaporated and partitioned the residues between EtOAc (50 ml) and 2N HCl (50 mL). Extracted the aqueous layer twice more with EtOAc (2 x 25 ml). Combined extracts, washed with brine (50 ml), dried with anhydrous magnesium sulfate, filtered and evaporated. A clear oil product (0.49 g, 86%) was obtained. Anal. ($C_{11}H_{17}NO_5$) C, H, N.

¹⁰ 1H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, 3H, $J=7.5$); 1.25 (s, 6H); 1.70-1.95 (m, 2H); 4.22-4.29 (m, 2H); 4.66 (dd, 1H, $J=4.6, 6.5$); 5.04 (dd, 2H, $J=5.0, 8.9$); 7.67 (bs, 1H).

Example 2

A lotion comprising the following composition may be prepared.

	(%)
95% Ethanol	80.0
a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	10.0
α-Tocopherol acetate	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
purified water	9.0
perfume and dye	q.s.

30 Into 95% ethanol are added a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, α-tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume and a dye. The resulting mixture is stirred and dissolved, and purified water is added to the mixture to obtain a transparent liquid lotion.

5 ml of the lotion may be applied once or twice per day to a site having marked baldness or alopecia.

Example 3

A lotion comprising the following composition shown may be prepared.

		(%)
	95% Ethanol	80.0
10	a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.005
15	Hinokitol	0.01
	Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
20	Purified water	19.0
25	Perfume and dye	q.s.

Into 95% ethanol are added a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, hinokitol, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye. The resulting mixture is stirred, and purified water is added to the mixture to obtain a transparent liquid lotion.

The lotion may be applied by spraying once to 4 times per day to a site having marked baldness or alopecia.

Example 4

An emulsion may be prepared from A phase and B phase having the following compositions.

(A phase)	(%)
Whale wax	0.5
Cetanol	2.0
Petrolatum	5.0

	Squalane	10.0
	Polyoxyethylene (10 mole) monostearate	2.0
	Sorbitan monooleate	1.0
5	A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.01
	(B phase)	(%)
10	Glycerine	10.0
	Purified water	69.0
	Perfume, dye, and preservative	q.s.

15 The A phase and the B phase are respectively heated and melted and maintained at 80°C. Both phases are then mixed and cooled under stirring to normal temperature to obtain an emulsion.

20 The emulsion may be applied by spraying once to four times per day to a site having marked baldness or alopecia.

Example 5

A cream may be prepared from A phase and B phase having the following compositions.

	(A Phase)	(%)
25	Fluid paraffin	5.0
	Cetostearyl alcohol	5.5
	Petrolatum	5.5
	Glycerine monostearate	33.0
30	Polyoxyethylene (20 mole) 2-octyldodecyl ether	3.0
	Propylparaben	0.3
	(B Phase)	(%)

	a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.8
5	Glycerine	7.0
	Dipropylene glycol	20.0
	Polyethylene glycol 4000	5.0
	Sodium Hexametaphosphate	0.005
10	Purified water	44.895

The A phase is heated and melted, and maintained at 70°C. The B phase is added into the A phase and the mixture is stirred to obtain an emulsion. The emulsion is then cooled to obtain a cream.

The cream may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 6

A liquid comprising the following composition may be prepared.

		(%)
	Polyoxyethylene butyl ether	20.0
	Ethanol	50.0
20	A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.001
25	Propylene glycol	5.0
	Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts)	0.4
30	Perfume	q.s.
	Purified water	q.s.

35 Into ethanol are added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a carboxylic acid or carboxylic acid isostere of an N-

heterocyclic ring compound having two or more heteroatoms in the ring, and perfume. The resulting mixture is stirred, and purified water is added to the mixture to obtain a liquid.

5 The liquid may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 7

A shampoo comprising the following composition may be prepared.

	(%)
Sodium laurylsulfate	5.0
Triethanolamine laurylsulfate	5.0
Betaine lauryldimethylaminoacetate	6.0
Ethylene glycol distearate	2.0
Polyethylene glycol	5.0
a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	5.0
Ethanol	2.0
Perfume	0.3
Purified water	69.7

25 Into 69.7 of purified water are added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethyl-aminoacetate. Then a mixture obtained by adding 5.0 g of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, 5.0 g of polyethylene glycol, and 2.0 g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume are successively added. The resulting mixture is heated and subsequently cooled to obtain a shampoo.

30 The shampoo may be used on the scalp once or twice per day.

Example 8

A patient is suffering from alopecia senilis. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 9

A patient is suffering from male pattern alopecia. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 10

A patient is suffering from alopecia areata. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 11

A patient is suffering from hair loss caused by skin lesions. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 12

A patient is suffering from hair loss caused by tumors. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the

same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 13

5 A patient is suffering from hair loss caused by a systematic disorder, such as a nutritional disorder or an internal secretion disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

10

Example 14

15 A patient is suffering from hair loss caused by chemotherapy. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

20

Example 15

25 A patient is suffering from hair loss caused by radiation. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same may, be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 16

30 A patient is suffering from a neurodegenerative disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or a pharmaceutical composition comprising the same is administered. It would be expected that the patient would improve their condition or recover.

Example 17

A patient is suffering from a neurological disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 18

A patient is suffering from stroke. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 19

A patient is suffering from Parkinson's Disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 20

A patient is suffering from Alzheimer's Disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 21

A patient is suffering from a peripheral neuropathy. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 22

A patient is suffering from amyotrophic lateral sclerosis. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions

comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 23

5 A patient is suffering from a spinal injury. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

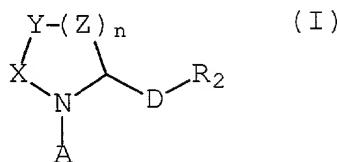
Example 24

10 A patient is at risk of suffering from a neurodegenerative disease or neurological disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or a pharmaceutical composition comprising the same is prophelactically administered. It would be expected that the patient would be prevented from some or all of the effects of the disease or disorder, or would significantly improve their condition or recover over patients who were not pre-treated.

15 The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

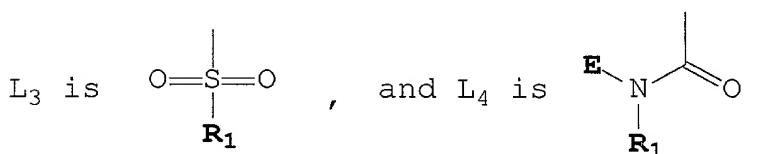
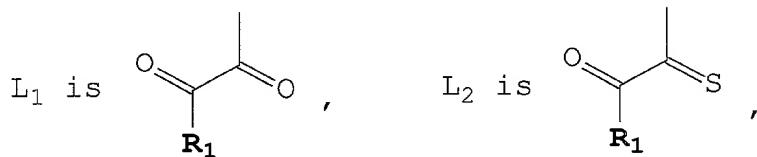
1. A compound of formula (I):



where

5 X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;
n is 1-3;
A is selected from the group consisting of L₁, L₂, L₃, or
10 L₄,

where



15 R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉, straight or branched chain alkyl or alkenyl, C₂-C₉, straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

R₂ is a carboxylic acid or a carboxylic acid isostere;

20 wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R³, where

R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano,

nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO₂R⁴ where R⁴ is 5 hydrogen or C₁-C₉ straight or branched chain alkyl or alkenyl; or a pharmaceutically acceptable salt, ester, or solvate thereof;

provided that:

10 R₁ is not substituted with both hydroxy and oxygen to form carboxy, or R₁ is not substituted with both alkoxy and oxygen to form alkoxy carbonyl, or R₁ is not substituted with both amine and oxygen to form amide;

further provided that:

15 when A is L₁ or L₂, and D is a bond, then R₂ is not COOH, or an amide;

further provided that:

when A is L₁, and R₁ is methyl, and D is a bond, then R₂ is not COOH;

further provided that:

20 when A is L₃, and R₁ is phenyl, methylphenyl, phenylmethyl, substituted or unsubstituted phenoxyphenyl, substituted naphthyl, or methoxyphenyl, and D is a bond, then R₂ is not COOH or an amide;

further provided that:

25 when A is L₃, and R₁ is phenyl, and D is a bond, then R₂ is not thiophenyl;

further provided that:

when A is L₃, and R₁ is phenyl, and D is oxyethyl, then R₂ is not an amide;

further provided that:

30 when A is L₃, and R₁ is substituted isoquinoline, and D is butyl,

then R₁ is not an amide;

further provided that:

when A is L₃ or L₄, and R₁ is unsubstituted or substituted phenyl, and D is C₁-C₃ alkyl or alkenyl,

then R₂ is not COOH, OH, or an amide;

further provided that:

5 when A is L₄, and R₁ is phenyl, halo-substituted phenyl, dimethylphenyl, substituted butyl, or methylphenyl, and D is a bond,

then R₂ is not COOH;

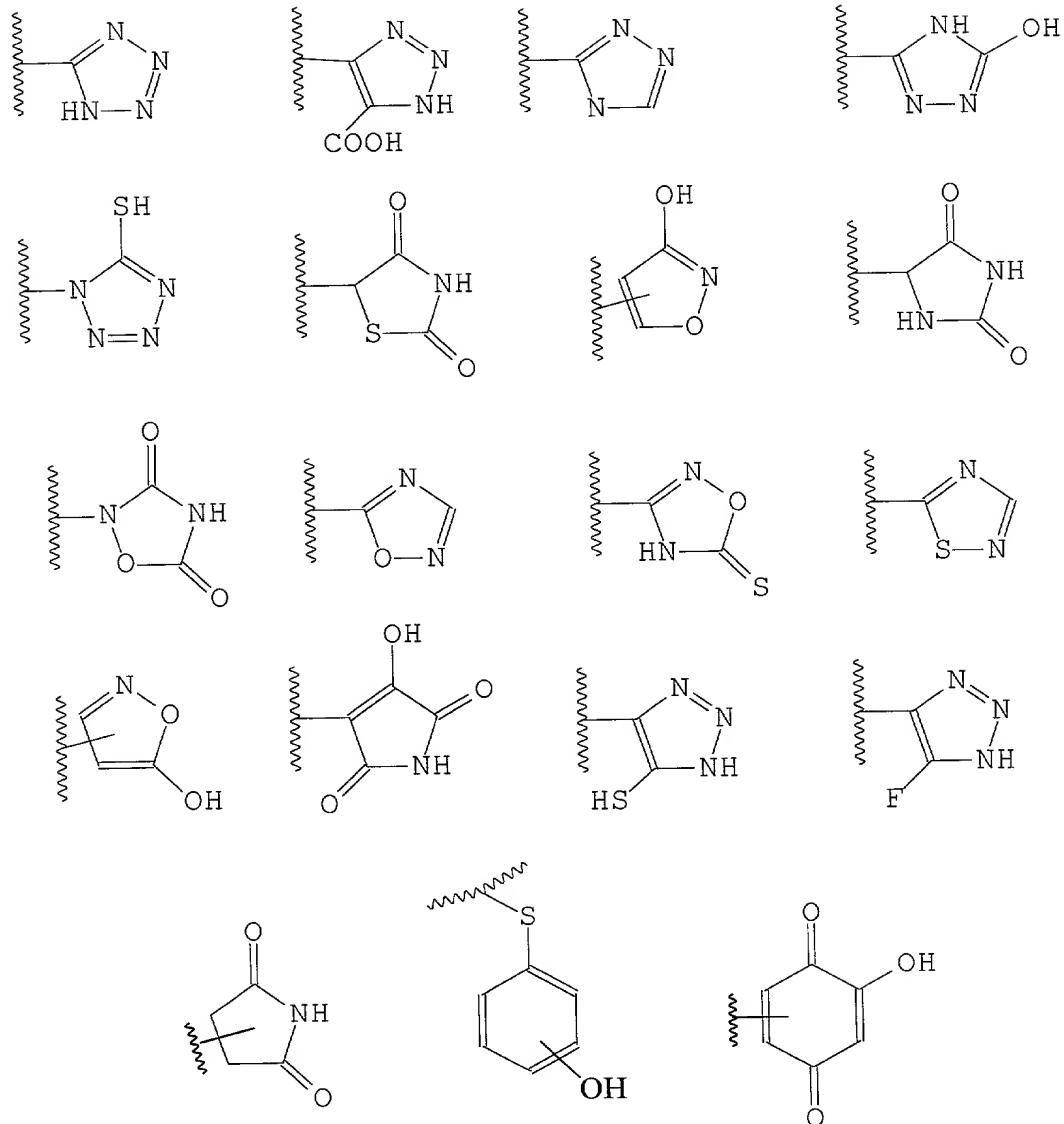
further provided that:

10 when A is L₄, and R₁ is cyano-substituted alkyl, and D is a bond,

then R₂ is not an amide.

2. The compound of claim 1, wherein the carboxylic acid isostere of R₂ is a carbocycle or heterocycle containing any combination of CH₂, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R³.

20 3. The compound of claim 1, wherein R₂ is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3 .

4. The compound of claim 1, wherein the carboxylic acid or
5 carboxylic acid isostere of R_2 is selected from the group
consisting of:

$-\text{COOH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{HNR}^3$, $-\text{PO}_2(\text{R}^3)_2$, $-\text{CN}$, $-\text{PO}_3(\text{R}^3)_2$, $-\text{OR}^3$, $-\text{SR}^3$, $-\text{NHCOR}^3$, $-\text{N}(\text{R}^3)_2$, $-\text{CON}(\text{R}^3)_2$, $-\text{CONH}(\text{O})\text{R}^3$, $-\text{CONHNHSO}_2\text{R}^3$, $-\text{COHNSO}_2\text{R}^3$, and $-\text{CONR}^3\text{CN}$.

10

5. The compounds, (2S)-1-(phenylmethyl) carbamoyl-2-hydroxymethyl (4-thiazolidine); (2S)-1-(1,1-dimethylpropyl) carbamoyl-2-(4-thiazolidine) tetrazole; (2S)-1-(phenylmethyl) carbamoyl-2-(4-thiazolidine) carbonitrile; (2S)-1-(1,1-dimethylpropyl) carbamoyl-2-(4-thiazolidine) tetrazole; 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylic acid; and (2S)-1-(3,3-dimethyl 1,2-dioxopropyl)-2-(3-thiazolidine) carboxylic acid..

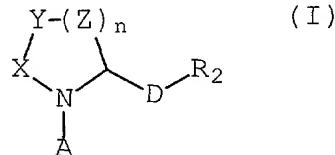
6. A pharmaceutical composition, comprising:

- a) an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring; and
- b) a pharmaceutically acceptable carrier.

25

7. The pharmaceutical composition of claim 6, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring comprises a compound of formula (I):

30



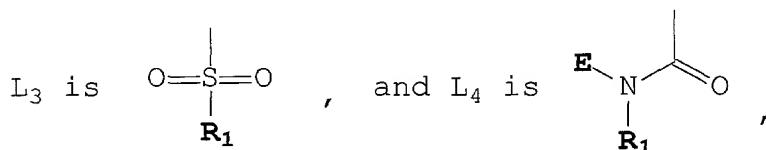
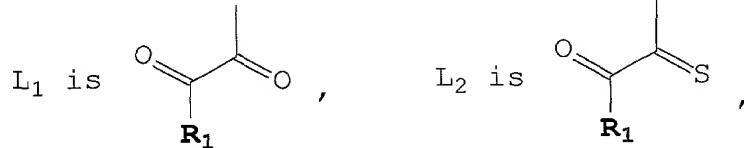
where

X, Y, and Z are independently selected from the group

consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

n is 1-3;

A is selected from the group consisting of L₁, L₂, L₃, or L₄,
5 where



R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉ straight or branched chain alkyl or alkenyl, C₂-C₉ straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

R₂ is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, or heterocycle is optionally substituted with one or more substituents selected from R³, where

R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO₂R⁴ where R⁴ is hydrogen or C₁-C₉ straight or branched chain alkyl or alkenyl;

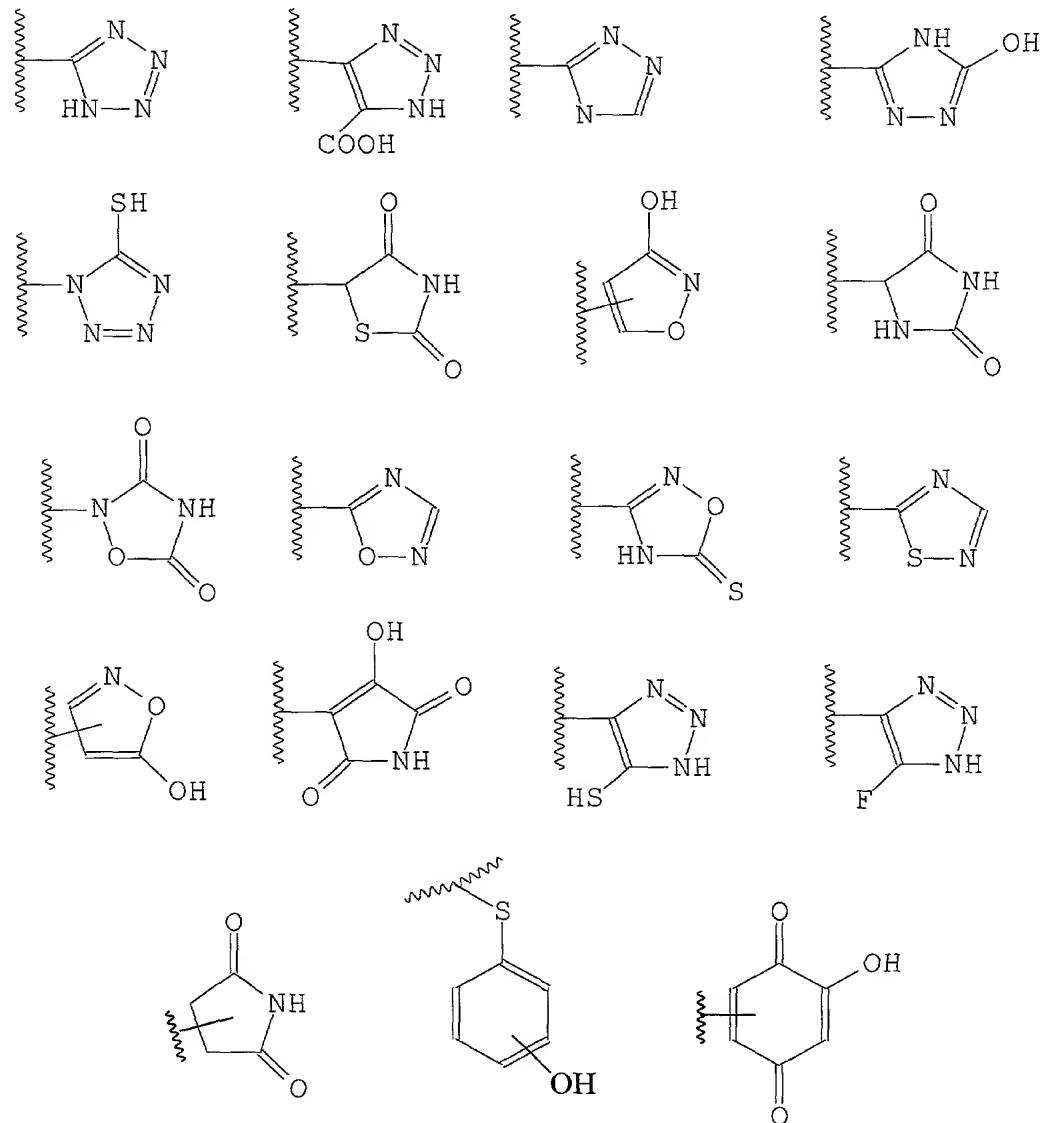
20 or a pharmaceutically acceptable salt, ester, or solvate thereof.

25 8. The pharmaceutical composition of claim 7, wherein R₂

is a carbocycle or heterocycle containing any combination of CH₂, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R³.

5

9. The pharmaceutical composition of claim 7, wherein R₂ is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R³.

10. The pharmaceutical composition of claim 7, wherein R₂ is selected from the group consisting of:

5 -COOH, -SO₃H, -SO₂HNR³, -PO₂(R³)₂, -CN, -PO₃(R³)₂, -OR³, -SR³,
-NHCOR³, -N(R³)₂, -CON(R³)₂, -CONH(O)R³, -CONHNHSO₂R³,
-COHNSO₂R³, and -CONR³CN.

10 11. The pharmaceutical composition of claim 7, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is selected from the group consisting of compounds 1-442, compound L, and compound M.

15 12. The pharmaceutical composition of claim 6, further comprising a neurotrophic factor different from formula (I).

20 13. The pharmaceutical composition of claim 12, wherein said neurotrophic factor different from formula (I) is selected from neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3 and neurotropin 4/5.

25 14. A method of treating a neurological disorder in an animal, comprising:

30 administering to the animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration.

15. The method of claim 14, wherein the neurological disorder is selected from the group consisting of peripheral neuropathies cause by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorders relating to neurodegeneration.

5

16. The method of claim 14, wherein the neurological disorder is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

10

17. The method of claim 14, wherein the neurological disorder is Alzheimer's disease.

15

18. The method of claim 14, wherein the neurological disorder is Parkinson's disease.

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19. The method of claim 14, wherein the neurological disorder is amyotrophic lateral sclerosis.

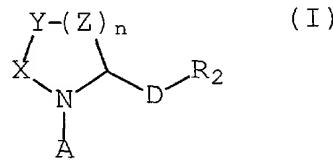
25

20. The method of claim 14, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is non-immunosuppressive.

25

21. The method of claim 14, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring comprises a compound of formula (I):

30



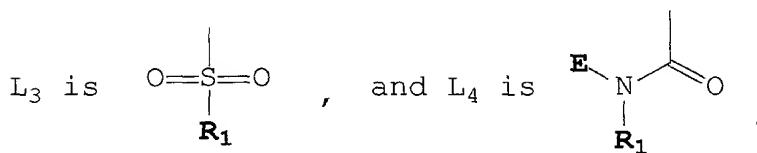
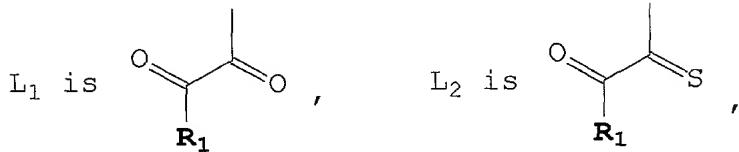
where

X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

n is 1-3;

5 A is selected from the group consisting of L₁, L₂, L₃, or L₄,

where



10 R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉, straight or branched chain alkyl or alkenyl, C₂-C₉, straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

15 D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

R₂ is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, or heterocycle is optionally substituted with one or more substituents selected from R³, where

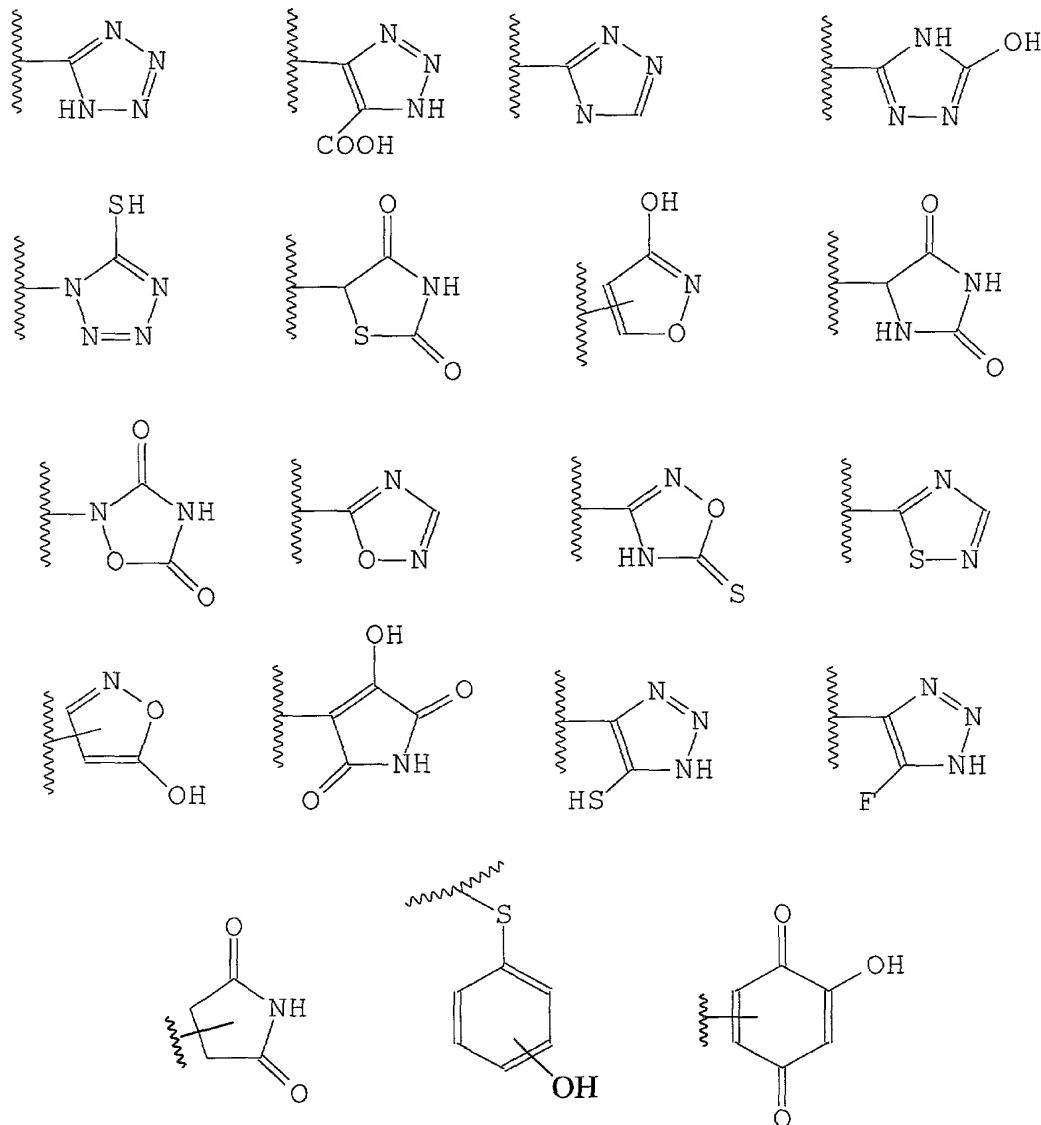
20 R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO₂R⁴ where R⁴ is hydrogen or C₁-C₉ straight or branched chain alkyl or alkenyl;

25 or a pharmaceutically acceptable salt, ester, or solvate thereof.

22. The method of claim 21, wherein R_2 is a carbocycle or heterocycle containing any combination of CH_2 , O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R^3 .

5

23. The method of claim 21, wherein R_2 is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3 .

24. The method of claim 21, wherein R_2 is selected from the group consisting of:

5 $-COOH$, $-SO_3H$, $-SO_2HNR^3$, $-PO_2(R^3)_2$, $-CN$, $-PO_3(R^3)_2$, $-OR^3$, $-SR^3$,
 $-NHCOR^3$, $-N(R^3)_2$, $-CON(R^3)_2$, $-CONH(O)R^3$, $-CONHNHSO_2R^3$,
 $-COHNSO_2R^3$, and $-CONR^3CN$.

10 25. The method of claim 14, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is selected from the group consisting of compounds 1-442, compound L, and compound M.

15 26. The method of claim 14, further comprising administering a neurotrophic factor different from formula (I).

20 27. The method of claim 26, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.

25 28. A method of stimulating growth of damaged peripheral nerves, comprising:

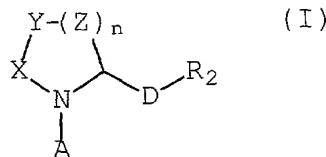
30 administering to damaged peripheral nerves an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring to stimulate or promote growth of the damaged peripheral nerves.

29. The method of claim 28, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is non-immunosuppressive.

5

30. The method of claim 28, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring comprises a compound of formula (I):

10



where

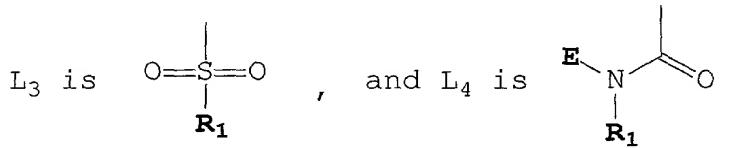
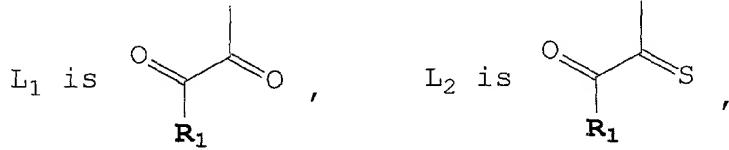
X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

15

n is 1-3;

A is selected from the group consisting of L₁, L₂, L₃, or L₄,

where



20

R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉, straight or branched chain alkyl or alkenyl, C₂-C₉, straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

25

D is selected from the group consisting of a bond, C₁-C₁₀, straight or branched chain alkyl, ethylene, and butylene;

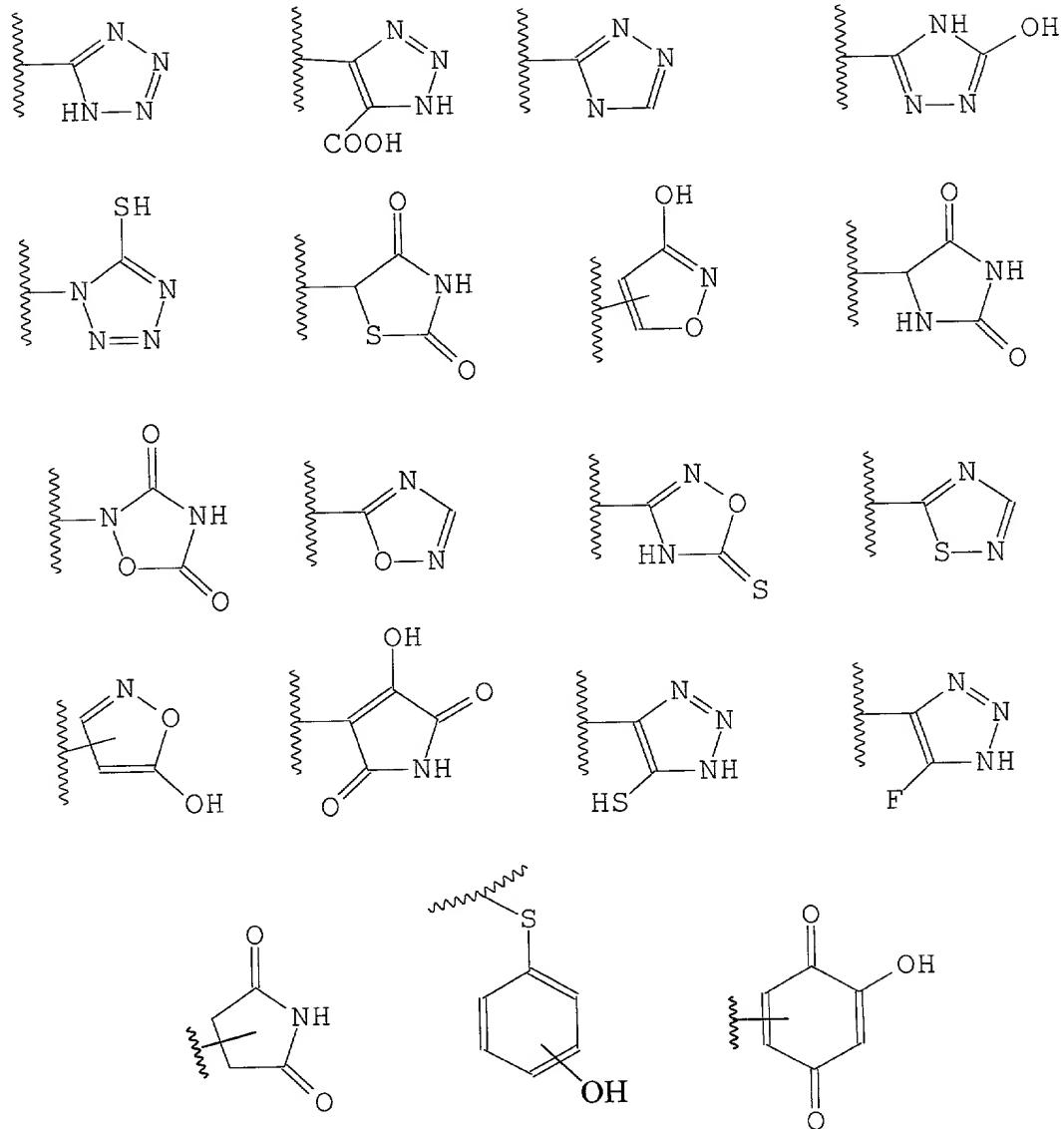
R₂ is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, or heterocycle is optionally substituted with one or more substituents selected from R³, where

5 R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO₂R⁴ where R⁴ is hydrogen or C₁-C₉ straight or branched chain alkyl or alkenyl;

10 or a pharmaceutically acceptable salt, ester, or solvate thereof.

15 31. The method of claim 30, wherein R₂ is a carbocycle or heterocycle containing any combination of CH₂, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R³.

20 32. The method of claim 30, wherein R₂ is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3 .

33. The method of claim 30, wherein R_2 is selected from the group consisting of:

5 $-COOH$, $-SO_3H$, $-SO_2HNR^3$, $-PO_2(R^3)_2$, $-CN$, $-PO_3(R^3)_2$, $-OR^3$, $-SR^3$,
 $-NHCOR^3$, $-N(R^3)_2$, $-CON(R^3)_2$, $-CONH(O)R^3$, $-CONHNHSO_2R^3$,
 $-COHNSO_2R^3$, and $-CONR^3CN$.

10 34. The method of claim 28, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is selected from the group consisting of compounds 1-442, compound L, and compound M.

15 35. The method of claim 28, further comprising administering a neurotrophic factor different from formula (I).

20 36. The method of claim 35, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.

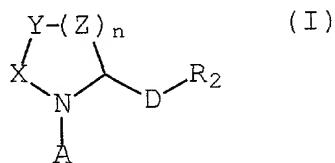
25 37. A method for promoting neuronal regeneration and growth in animals, comprising:

30 administering to an animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring to promote neuronal regeneration.

35 38. The method of claim 37, wherein the carboxylic acid or

carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is non-immunosuppressive.

5 39. The method of claim 37, wherein the Carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring comprises a compound of formula (I):



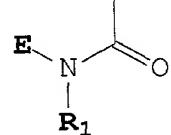
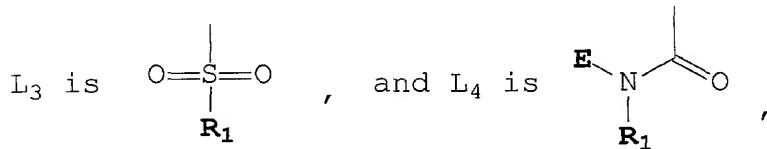
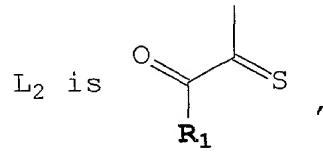
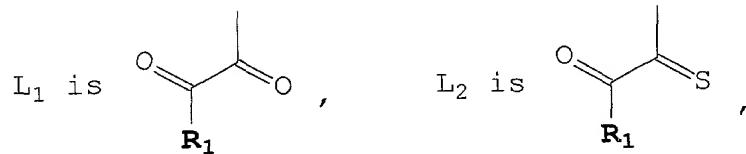
10 where

X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

n is 1-3;

15 A is selected from the group consisting of L₁, L₂, L₃, or L₄,

where



20 R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉ straight or branched chain alkyl or alkenyl, C₂-C₉ straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

25 R₂ is a carboxylic acid or a carboxylic acid isostere;

wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, or heterocycle is optionally substituted with one or more substituents selected from R³, where

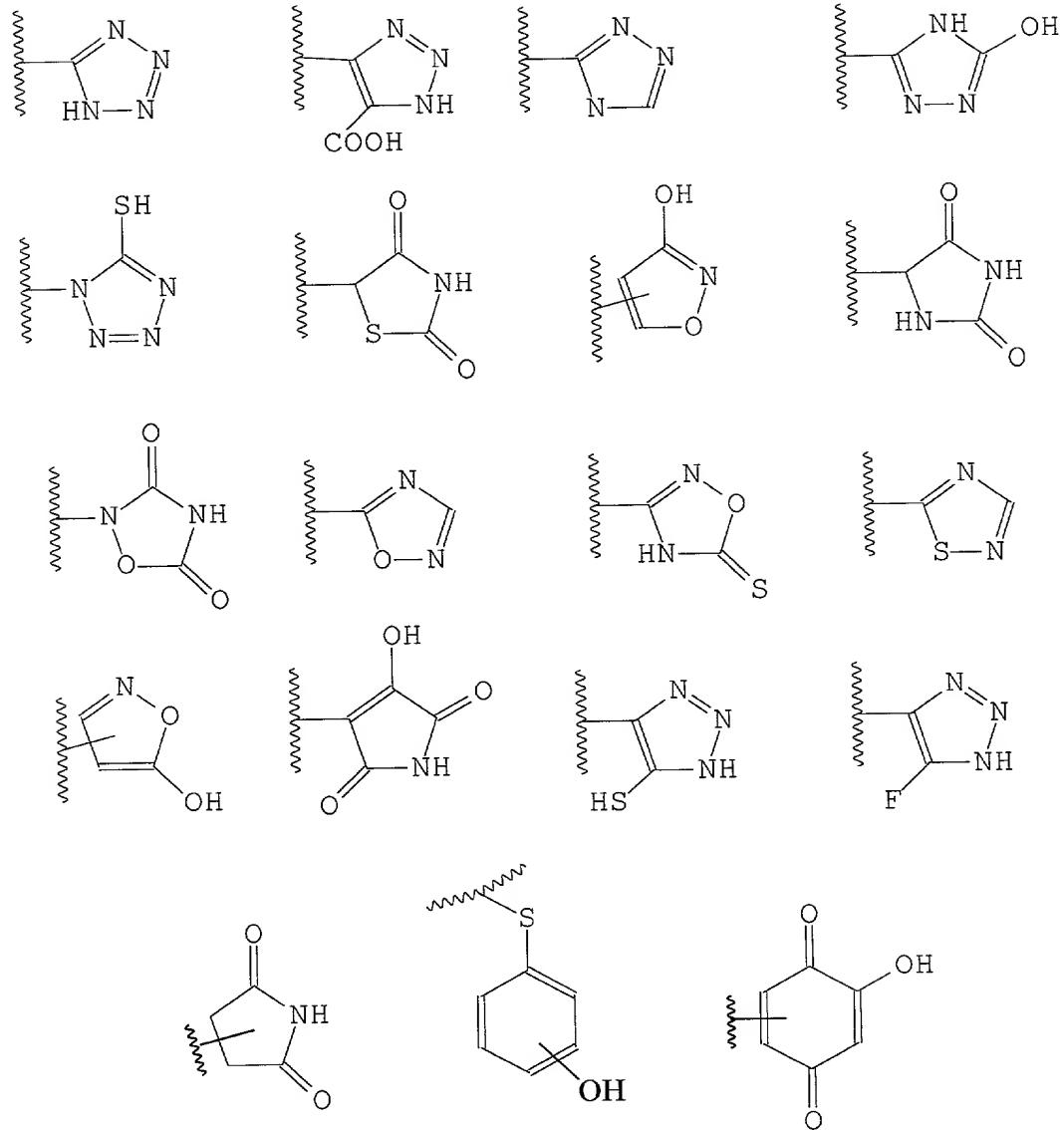
R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO₂R⁴ where R⁴ is

hydrogen or C₁-C₉ straight or branched chain alkyl or alkenyl;

or a pharmaceutically acceptable salt, ester, or solvate thereof.

40. The method of claim 39, wherein R₂ is a carbocycle or heterocycle containing any combination of CH₂, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R³.

41. The method of claim 39, wherein R₂ is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3 .

42. The method of claim 39, wherein R_2 is selected from the group consisting of:

-COOH, -SO₃H, -SO₂HNR³, -PO₂(R³)₂, -CN, -PO₃(R³)₂, -OR³, -SR³, -NHCOR³, -N(R³)₂, -CON(R³)₂, -CONH(O)R³, -CONHNHSO₂R³, -COHSO₂R³, and -CONR³CN.

43. The method of claim 37, wherein the N-heterocyclic carboxylic acid compound is selected from the group consisting of compounds 1-442, compound L, and compound M.

44. The method of claim 37, further comprising administering a neurotrophic factor different from formula (I).

45. The method of claim 44, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.

46. A method for preventing neurodegeneration in an animal, comprising:

administering to an animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring to prevent neurodegeneration.

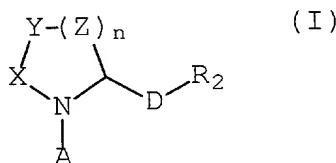
47. The method of claim 46, wherein the neurodegeneration is Alzheimer's disease.

48. The method of claim 46, wherein the neurodegeneration is Parkinson's disease.

49. The method of claim 46, wherein the neurodegeneration is amyotrophic lateral sclerosis.

50. The method of claim 46, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is non-immunosuppressive.

10 51. The method of claim 46, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring comprises a compound of formula (I):



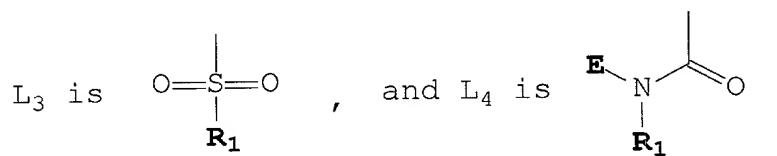
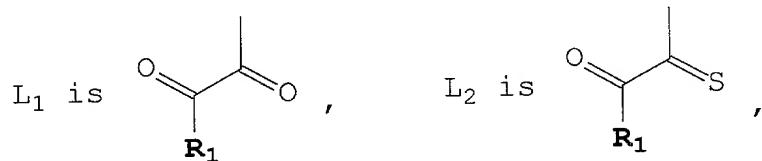
15 where

X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

20 n is 1-3;

A is selected from the group consisting of L₁, L₂, L₃, or L₄,

where



R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉ straight or branched chain alkyl or alkenyl, C₂-C₉ straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

5 D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

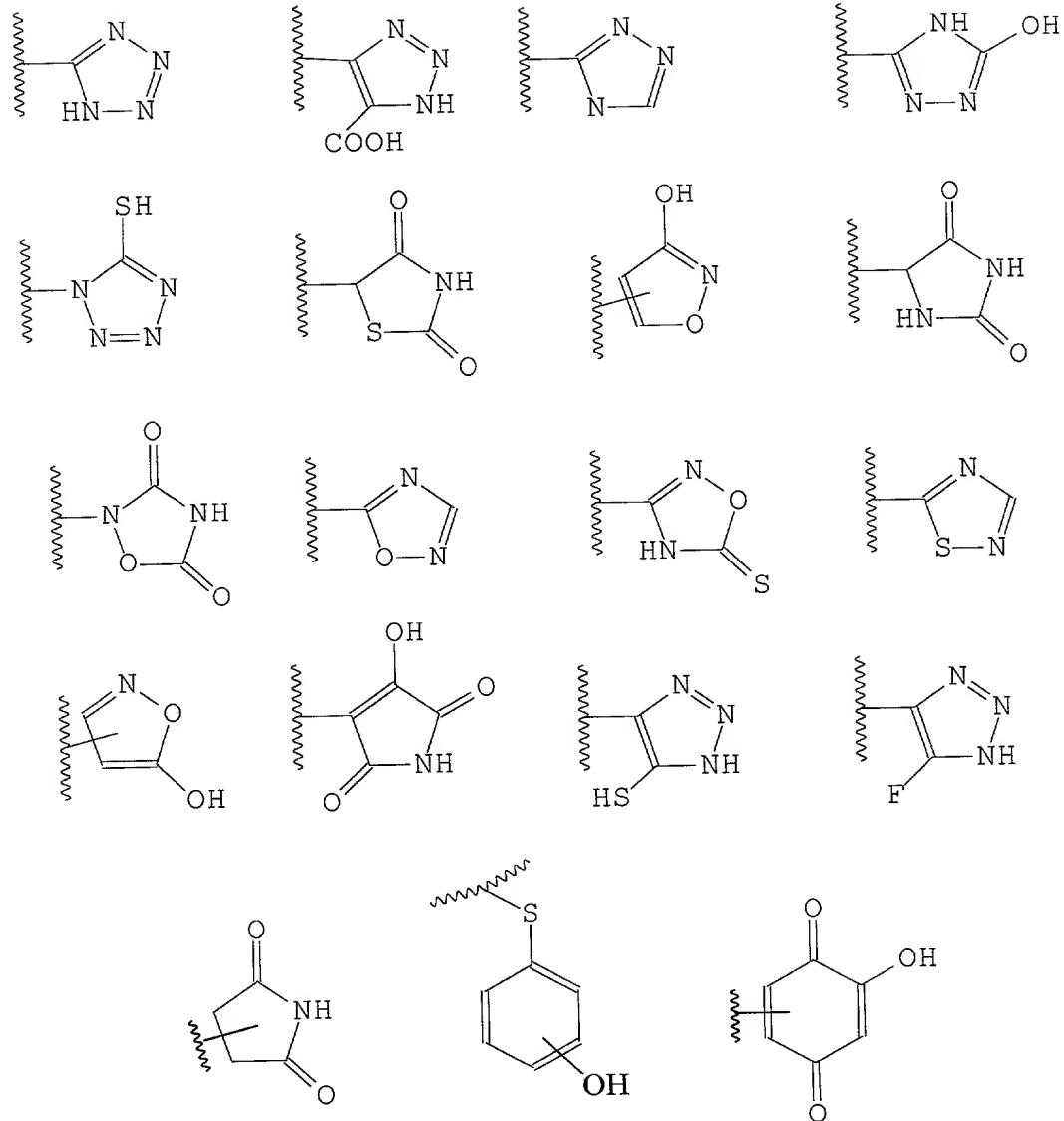
R₂ is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, or heterocycle is optionally substituted with one or more substituents selected from R³, where

10 R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO₂R⁴ where R⁴ is hydrogen or C₁-C₉ straight or branched chain alkyl or alkenyl;

15 or a pharmaceutically acceptable salt, ester, or solvate thereof.

20 52. The method of claim 51, wherein R₂ is a carbocycle or heterocycle containing any combination of CH₂, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R³.

25 53. The method of claim 51, wherein R₂ is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R³.

54. The method of claim 51, wherein R₂ is selected from the group consisting of:

-COOH, -SO₃H, -SO₂HNR³, -PO₂(R³)₂, -CN, -PO₃(R³)₂, -OR³, -SR³, -NHCOR³, -N(R³)₂, -CON(R³)₂, -CONH(O)R³, -CONHNHSO₂R³, -COHNSO₂R³, and -CONR³CN.

10 55. The method of claim 46, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is selected from the group consisting of compounds 1-442, compound L, and compound M.

15 56. The method of claim 46, further comprising administering a neurotrophic factor different from formula (I).

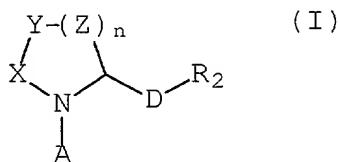
20 57. The method of claim 56, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.

25 58. A method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring.

30 35 59. The method of claim 58, wherein the carboxylic acid or

carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is non-immunosuppressive.

5 60. The method of claim 58, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is a compound of formula (I):



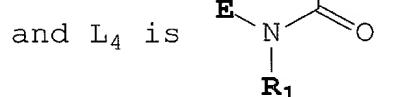
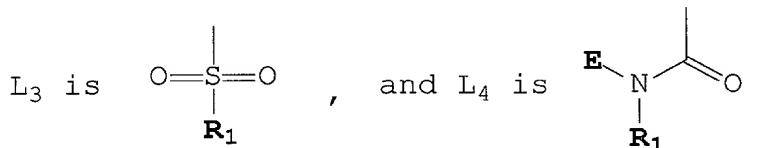
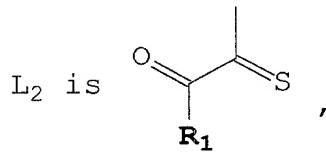
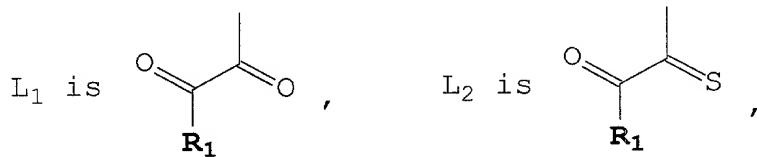
10 where

X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

n is 1-3;

A is selected from the group consisting of L₁, L₂, L₃, or L₄,

where



20 R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉, straight or branched chain alkyl or alkenyl, C₂-C₉, straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

25 R₂ is a carboxylic acid or a carboxylic acid isostere;

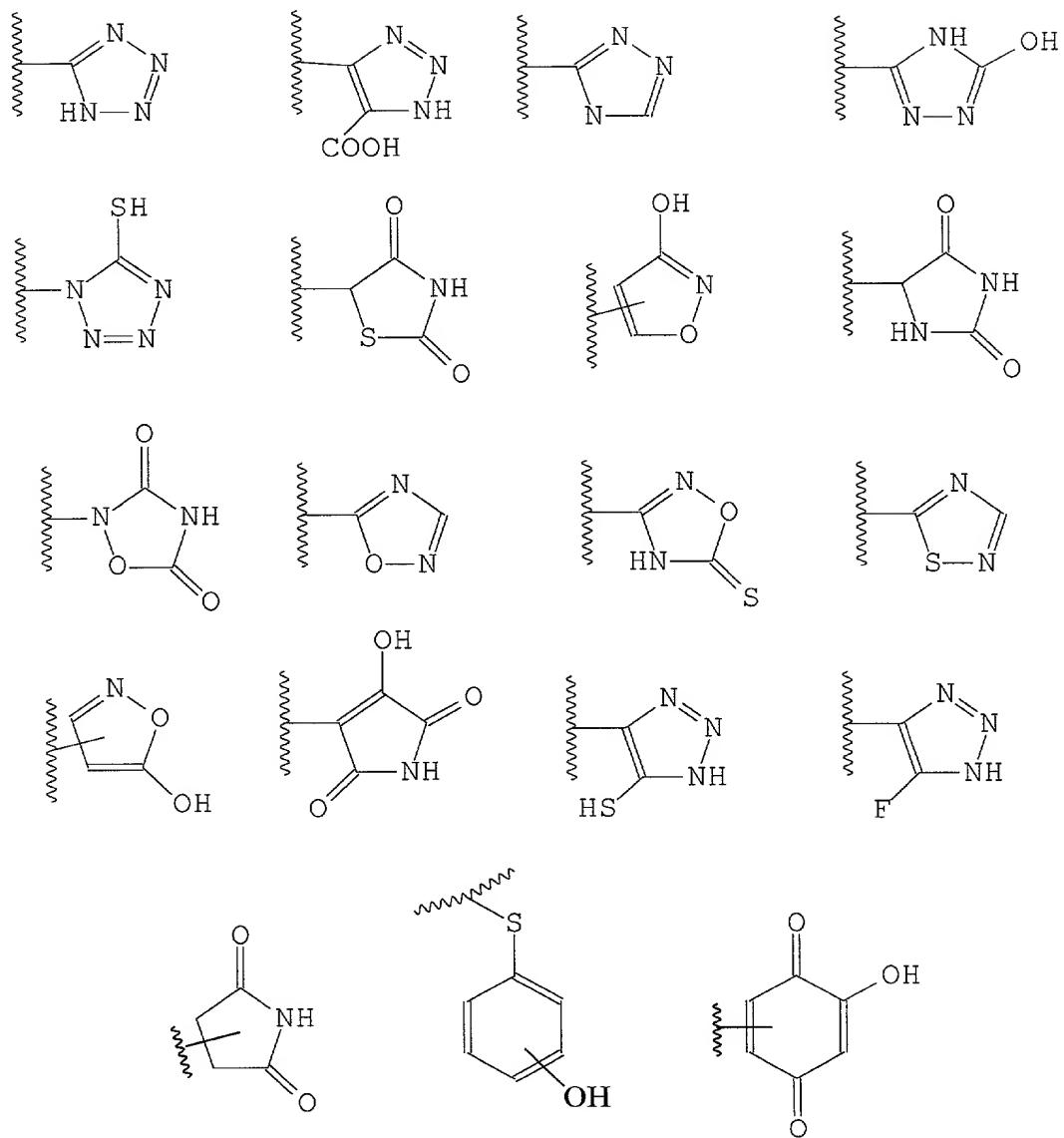
wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R³, where

5 R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO₂R⁴ where R⁴ is hydrogen or C₁-C₉ straight or branched chain alkyl or alkenyl;

10 or a pharmaceutically acceptable salt, ester, or solvate thereof.

15 61. The method of claim 60, wherein R₂ is a carbocycle or heterocycle containing any combination of CH₂, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R³.

20 62. The method of claim 60, wherein R₂ is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R³.

63. The method of claim 60, wherein R₂ is selected from the
5 group consisting of

-COOH, -SO₃H, -SO₂HNR³, -PO₂(R³)₂, -CN, -PO₃(R³)₂, -OR³, -SR³,
-NHCOR³, -N(R³)₂, -CON(R³)₂, -CONH(O)R³, -CONHNHSO₂R³,
-COHNSO₂R³, and -CONR³CN.

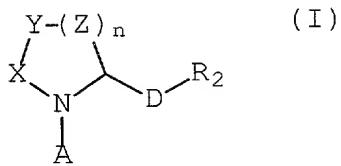
10 64. The method of claim 58, wherein the carboxylic acid or
carboxylic acid isostere of an N-heterocyclic ring compound
having two or more heteroatoms in the ring is selected from
the group consisting of compounds 1-442, compound L, and
compound M.

15 65. A pharmaceutical composition comprising:

(i) an effective amount of a carboxylic acid or
carboxylic acid isostere of an N-heterocyclic ring
compound having two or more heteroatoms in the
ring for treating alopecia or promoting hair
growth in an animal; and
(ii) a pharmaceutically acceptable carrier.

20 66. The pharmaceutical composition of claim 65, wherein the
carboxylic acid or carboxylic acid isostere of an N-
heterocyclic ring compound having two or more heteroatoms in
the ring is non-immunosuppressive.

25 67. The composition of claim 65, wherein the carboxylic acid
or carboxylic acid isostere of an N-heterocyclic ring
compound having two or more heteroatoms in the ring is a
compound of formula (I):



where

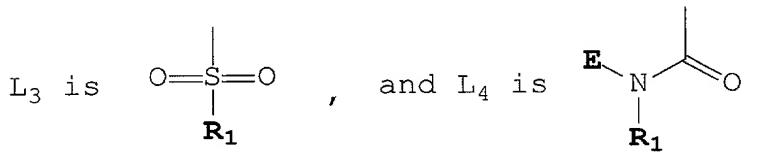
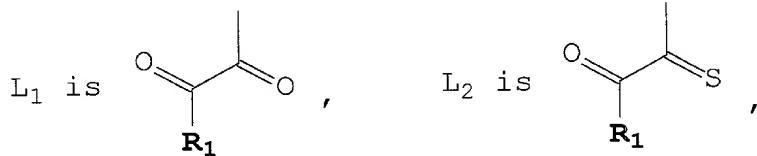
X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

5

n is 1-3;

A is selected from the group consisting of L₁, L₂, L₃, or L₄,

where



10 R₁ and E are independently selected from the group consisting of hydrogen, C₁-C₉ straight or branched chain alkyl or alkenyl, C₂-C₉ straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

15

D is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkyl, ethylene, and butylene;

R₂ is a carboxylic acid or a carboxylic acid isostere;

20 wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R³, where

R³ is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C₁-C₆ straight or branched chain alkyl,

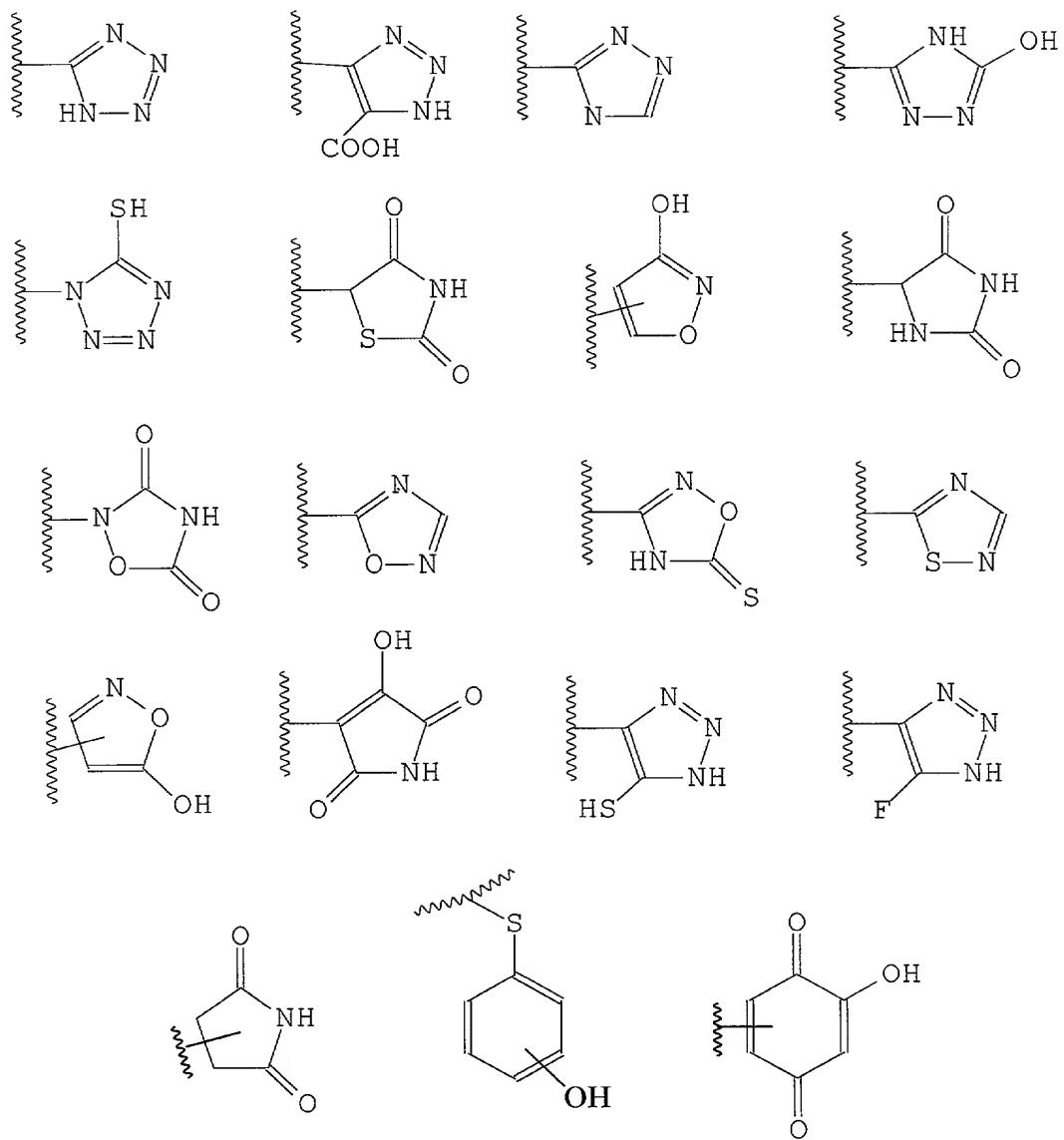
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C_2-C_6 straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO_2R^4 where R^4 is hydrogen or C_1-C_9 straight or branched chain alkyl or alkenyl;

5 or a pharmaceutically acceptable salt, ester, or solvate thereof.

68. The composition of claim 67, wherein R_2 is a carbocycle or heterocycle containing any combination of CH_2 , O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R^3 .

69. The composition of claim 67, wherein R_2 is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3 .

5 70. The composition of claim 67, wherein R_2 is selected from the group consisting of:

-COOH, $-SO_3H$, $-SO_2HNR^3$, $-PO_2(R^3)_2$, -CN, $-PO_3(R^3)_2$, $-OR^3$, $-SR^3$, $-NHCOR^3$, $-N(R^3)_2$, $-CON(R^3)_2$, $-CONH(O)R^3$, $-CONHNHSO_2R^3$, $-COHNSO_2R^3$, and $-CONR^3CN$.

10 71. The composition of claim 65, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is selected from the group consisting of compounds 1-442, compound L, and compound M.

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ABSTRACT OF THE DISCLOSURE

The present invention is directed to novel carboxylic acids and isosteres of heterocyclic ring compounds which have multiple heteroatoms within the heterocyclic ring, novel derivatives containing N-linked diketos, sulfonamides, ureas and carbamates attached thereto, their preparation and use for treating neurological disorders including physically damaged nerves and neurodegenerative diseases, as well as for treating alopecia and promoting hair growth.

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FIG. 1

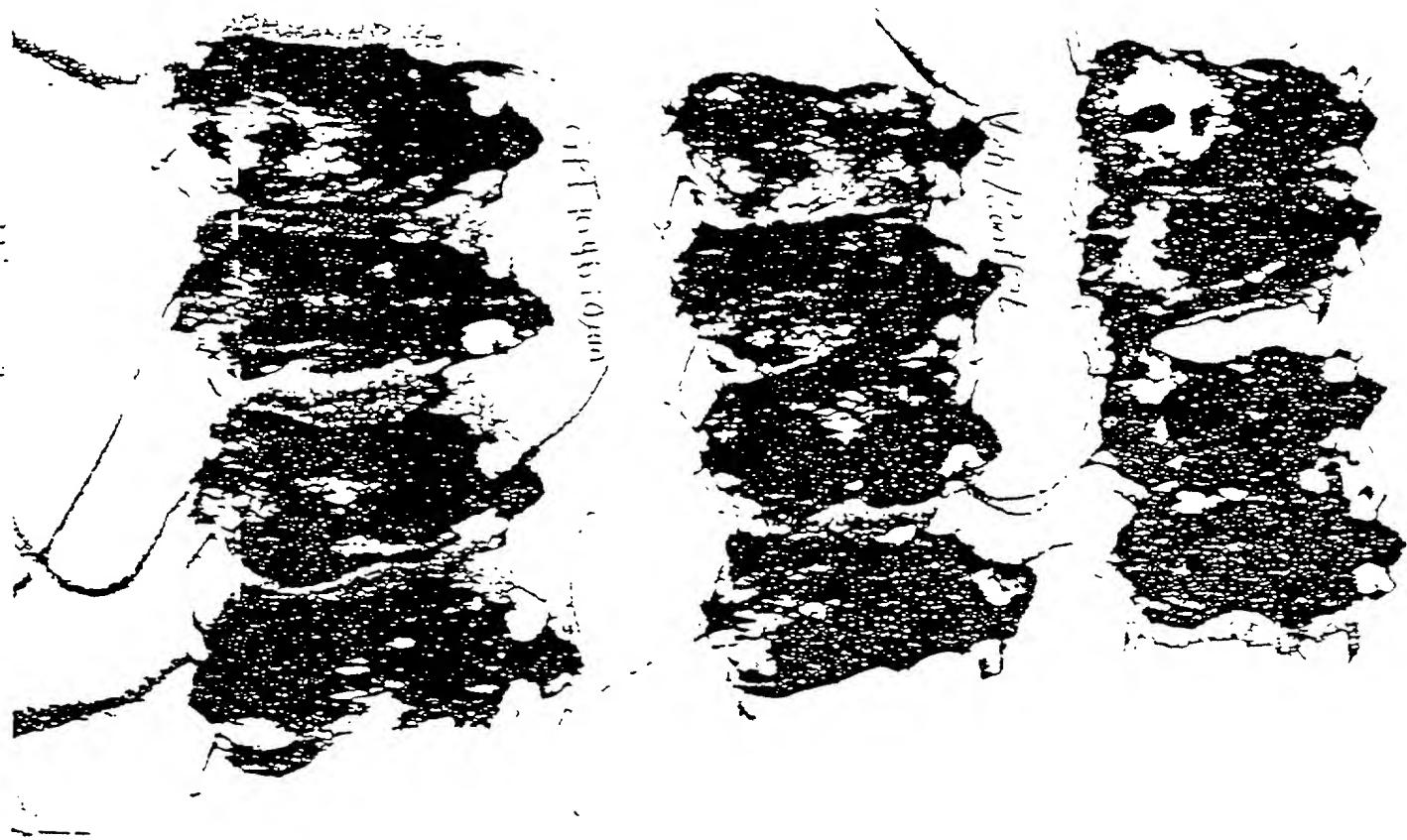
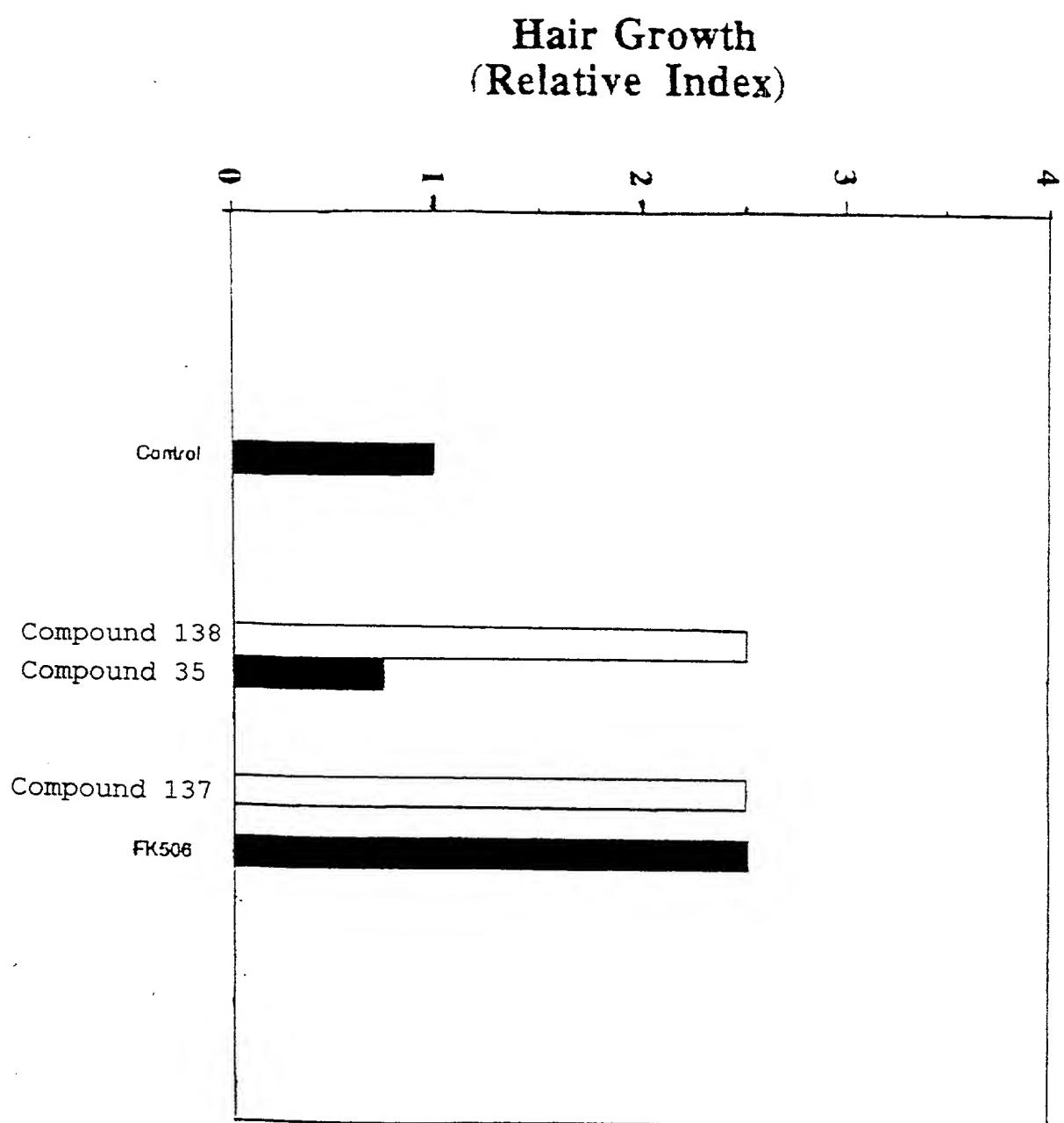


FIG. 2



Promotion of Hair Growth by Neuroimmunophilin Ligands

Fig. 3



DECLARATION FOR PATENT APPLICATION

Atty Docket AR138-X

As the below-named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our name.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:
MULTIPLE HETEROATOM CONTAINING HETEROCYCLIC RING COMPOUNDS SUBSTITUTED WITH CARBOXYLIC ACIDS AND ISOSTERES THEREOF

the specification of which: (check one)

[X] is attached hereto. [] was filed on _____, as Serial No. _____, and was amended on _____ 19 (if applicable).

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the patentability of this application as defined by 37 CFR § 1.56.

We hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed

(Application No.)	(Country)	(Day/Month/Year Filed)	[] []
(Application No.)	(Country)	(Day/Month/Year Filed)	Yes No [] []

We hereby appoint Gary M. Nath, Reg. No. 26,965; Irvin A. Lavine, Reg. No. 16,838; Karen Lee Orzechowski, Reg. No. 31,621; Harold L. Novick, Reg. No. 26,011; Suet M. Chong, Reg. No. 38,104; Patricia M. Drost, Reg. No. 29,790; Todd L. Juneau, Reg. No. 40,669; Lee C. Heiman, Reg. No. P-41,827; Donald M. Sandler, Reg. No. 19,237 and Robert G. Lev, Reg. No. 30,280 as our attorneys to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith.

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We hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by 35 U.S.C. § 112, first paragraph, we acknowledge the duty to disclose material information as defined in 37 CFR § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. Application Serial No.)	(U.S. Filing Date)	(Status—patented, pending, abandoned)
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(U.S. Application Serial No.)	(U.S. Filing Date)	(Status—patented, pending, abandoned)
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We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's Signature _____ Date _____

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Inventor's Signature _____ Date _____

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